COMBINATION OF AN ALLOSTERIC INHIBITOR OF MATRIX METALLOPROTEINASE-13 WITH A SELECTIVE INHIBITOR OF CYCLOOXYGENASE-2 THAT IS NOT CELECOXIB OR VALDECOXIB

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CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of priority from United States Provisional Patent Application Number 60/396,901, filed July 17, 2002.

FIELD OF THE INVENTION

This invention provides a combination of an allosteric inhibitor of matrix metalloproteinase-13 with a selective inhibitor of cyclooxygenase-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, a pharmaceutical composition comprising the combination, and methods of using the combination to treat diseases characterized by connective tissue breakdown, including cartilage damage, and inflammation or pain. Such diseases include arthritis, heart failure, multiple sclerosis, atherosclerosis, and osteoporosis.

BACKGROUND OF THE INVENTION

More than 23 million Americans have some form of arthritis. Among the various forms of arthritis, osteoarthritis ("OA") is the most prevalent, affecting 21 million Americans. Characterized by the degeneration of joint cartilage and adjacent bone, OA is a chronic disorder that can cause pain and stiffness. Rheumatoid arthritis ("RA"), which affects more than 2.1 million Americans, is an autoimmune disease that affects joint lining, cartilage and bones.

Aspirin and conventional nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, diclofenac, and naproxen are the primary agents used to treat OA- and RA-related pain. These agents inhibit prostaglandin release by blocking

cyclooxygenase-mediated conversion of cell membrane lipids from arachidonic acid.

Two forms of COX are now known, a constitutive isoform usually named cyclooxygenase-1 ("COX-1") and an inducible isoform usually named cyclooxygenase-2 ("COX-2"), the latter of which expression is upregulated at sites of inflammation. COX-1 appears to play a physiological role and to be responsible for gastrointestinal and renal protection. On the other hand, COX-2 appears to play a pathological role and is believed to be the predominant isoform present in inflammation conditions. The therapeutic use of conventional COX inhibitors, which are typically nonselective inhibitors of both COX-1 and COX-2, is limited due to drug associated side effects, including life threatening ulceration and renal toxicity. Compounds that selectively inhibit COX-2 would exert anti-inflammatory effects without the adverse side effects associated with COX-1 inhibition.

Valdecoxib is a COX-2 specific inhibitor that was approved in 2001 by the United States Food and Drug Administration ("FDA") for treating the signs and symptoms of osteoarthritis (OA) and adult rheumatoid arthritis (RA); and the treatment of pain associated with menstrual cramping. Valdecoxib tablets are marketed under the tradename BEXTRA®. In a combined analysis of various clinical studies with valdecoxib, valdecoxib was well tolerated with an overall upper gastrointestinal safety profile (ulcers, perforations, obstructions and GI bleeds) significantly better than the conventional NSAIDs studied such as ibuprofen, diclofenac and naproxen.

Matrix metalloproteinases ("MMPs") are naturally-occurring enzymes found in most mammals. Stromelysin-1 and gelatinase A are members of the matrix metalloproteinases (MMP) family. Other members include fibroblast collagenase (MMP-1), neutrophil collagenase (MMP-8), gelatinase B (92 kDa gelatinase) (MMP-9), stromelysin-2 (MMP-10), stromelysin-3 (MMP-11), matrilysin (MMP-7), collagenase 3 (MMP-13), and other newly discovered membrane-associated matrix metalloproteinases.

Over-expression or activation of MMPs, or an imbalance between MMPs and their endogenous inhibitors, namely tissue inhibitors of metalloproteinases

("TIMPs"), have been suggested as factors in the pathogenesis of diseases characterized by the breakdown of extracellular matrix or connective tissues. These diseases include rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, multiple sclerosis, gingivitis, corneal epidermal and gastric ulceration, atherosclerosis, neointimal proliferation which leads to restenosis and ischemic heart failure, and tumor metastasis.

A major limitation on the use of currently known MMP inhibitors is their lack of specificity for any particular MMP enzyme. Recent data has established that specific MMP enzymes are associated with some diseases, with no effect on others. The MMPs are generally categorized based on their substrate specificity, and indeed the collagenase subfamily of MMP-1, MMP-8, and MMP-13 selectively cleave native interstitial collagens, and thus are associated only with diseases linked to such interstitial collagen tissue. This is evidenced by the recent discovery that MMP-13 alone is over expressed in breast carcinoma, while MMP-1 alone is over expressed in papillary carcinoma (see Chen et al., *J. Am. Chem. Soc.*, 2000;122:9648-9654).

Another major limitation of currently known MMP inhibitors related to their lack of specificity for any particular MMP enzyme is their production of undesirable side effects related to inhibition of multiple MMP enzymes and/or tumor necrosis factor-alpha converting enzyme ("TACE"). One example of such a side effect is musculoskeletal syndrome ("MSS").

There appears to be few selective inhibitors of MMP-13 reported. A compound named WAY-170523 has been reported by Chen et al., supra., 2000, and a few other compounds are reported in PCT International Patent Application Publication Number WO 01/63244 A1, as allegedly selective inhibitors of MMP-13. Further, United States Patent Number 6,008,243 discloses inhibitors of MMP-13. These inhibitors contain functional groups that ligate, coordinate, or bind the catalytic zinc cation on MMP-13. However, selectivity in these cases can mean only a 5-fold or 10-fold greater inhibition of MMP-13 versus as few as one other MMP enzyme. Further, no selective or non-allosteric inhibitor of MMP-13 has been marketed for the treatment of any disease in any mammal.

Applicant has previously discovered highly selective inhibitors of MMP-13 that show promising pharmacological and pharmacokinetic activity in vivo. These inhibitors have been the subject of previously filed patent applications.

Applicant's inhibitors are more selective than prior art inhibitors for MMP-13 versus other MMP enzymes, both in terms of relative potencies and in terms of the numbers of the other MMP enzymes. For example, some of Applicant's inhibitors have shown 100-fold or greater selectivity with MMP-13 versus five or more other MMP enzymes, and further have shown efficacy in animal models of osteoarthritis.

The observed selectivity of Applicant's inhibitors may be attributed to the inhibitors' binding to MMP-13 at an allosteric site and, further, to a binding mode which does not involve binding to the enzyme's catalytic zinc. Prior to Applicant's allosteric MMP-13 inhibitors, it is believed that all prior art MMP-13 inhibitors bound to an MMP enzyme's catalytic zinc and occupied the MMP enzyme's substrate binding site. This latter binding mode was erroneously believed by others to be necessary for MMP-13 inhibitor potency.

Applicant's discovery that a combination of an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with a selective inhibitor of cyclooxygenase-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, is particularly useful for treating diseases characterized by damage to connective tissue such as cartilage damage. All that is required to treat diseases characterized by damage to connective tissue such as cartilage damage, including osteoarthritis, heart failure, multiple sclerosis, atherosclerosis, or osteoporosis in a mammal according to the invention is to administer to the mammal in need of treatment a therapeutically effective amount of the combination, wherein the combination comprises an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of cyclooxygenase-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib. As will be discussed below, the instant combination of an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with a selective inhibitor of cyclooxygenase-2, or a pharmaceutically acceptable salt

thereof, that is not celecoxib or valdecoxib, possesses many advantages over any combination of a prior art selective inhibitor of MMP-13 with a COX-2 inhibitor.

SUMMARY OF THE INVENTION

This invention provides a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

Another invention embodiment is a combination, comprising etoricoxib, or a pharmaceutically acceptable salt thereof, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

Another invention embodiment is a combination, comprising rofecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

Other invention embodiments are:

1. A combination, comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

Other invention embodiments include:

2. A combination, comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13 that comprises a hydrophobic group and first and second hydrogen bond acceptors, wherein:

(a) the relative positions of centroids of the above features are defined by the following Cartesian coordinates in Å:

(i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;

(ii) second hydrogen bond acceptor, 5.08, 2.23, 0.0;

(iii) first hydrophobic group, -1.52, -3.06, -0.23; and

(b) tolerances in the positions of the hydrophobic group and the hydrogen bond acceptors are ± 1.0 Å and ± 1.5 Å respectively.

3. A combination, comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13 that comprises first and second hydrophobic groups and first and second hydrogen bond acceptors, wherein:

(a) the relative positions of centroids of the above features are defined by the following Cartesian coordinates in Å:

(i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;

(ii) second hydrogen bond acceptor, 5.08, 2.23, 0.0;

(iii) first hydrophobic group, –1.52, -3.06, -0.23;

(iv) second hydrophobic group, 9.07, 0.00, 0.00; and

(b) tolerances in the positions of the hydrophobic groups and the hydrogen bond acceptors are ± 1.0 Å and ± 1.5 Å respectively.

4. A combination, comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13 that comprises a hydrophobic group and first, second and third hydrogen bond acceptors, wherein:

(a) the relative positions of centroids of the above features are defined by the following Cartesian coordinates in Å:

(i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;

(ii) second hydrogen bond acceptor, 5.08, 2.23, 0.0;

(iii) third hydrogen bond acceptor, 7.15, 0.80, 0.00;

(iv) first hydrophobic group, -1.52, -3.06, -0.23; and

(b) tolerances in the positions of the hydrophobic group and the hydrogen bond acceptors are ± 1.0 Å and ± 1.5 Å respectively.

5. A combination, comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13 that comprises first and second hydrophobic groups and first, second and third hydrogen bond acceptors, wherein:

(a) the relative positions of centroids of the above features are defined by the following Cartesian coordinates in Å:

(i) first hydrogen bond acceptor, 0.00, 0.00, 0.00;

(ii) second hydrogen bond acceptor, 5.08, 2.23, 0.0;

(iii) third hydrogen bond acceptor, 7.15, 0.80, 0.00;

(iv) first hydrophobic group, -1.52, -3.06, -0.23;

(v) second hydrophobic group, 9.07, 0.00, 0.00; and

(b) tolerances in the positions of the hydrophobic groups and the hydrogen bond acceptors are ± 1.0 Å and ± 1.5 Å respectively.

6. A combination, comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13 that comprises

a monocyclic, bicyclic, or tricyclic scaffold, wherein the bicyclic scaffold comprises a first ring fused to a second ring and the tricyclic scaffold comprises a first ring fused to a second ring, which is in turn fused to a third ring;

first and second hydrogen bond acceptors; and

first and second hydrophobic groups connected by linker chains to the scaffold, a cyclic structure forming part of the scaffold being located between the first and second hydrogen bond acceptors, and the hydrogen bond acceptors and hydrophobic groups being arranged so that when the inhibitor binds to MMP-13:

the first and second hydrogen bond acceptors interact respectively with the backbone NH's of Thr245 and Thr 247;

the first hydrophobic group locates within the S1' channel; and

the second hydrophobic group is open to solvent.

7. A combination, comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13 that comprises

a monocyclic, bicyclic, or tricyclic scaffold, wherein the bicyclic scaffold comprises a first ring fused to a second ring and the tricyclic scaffold comprises a first ring fused to a second ring, which is in turn fused to a third ring;

first, second and third hydrogen bond acceptors; and

a hydrophobic group connected by a linker chain to the scaffold, a cyclic structure forming part of the scaffold being located between the first and

second hydrogen bond acceptors, and the hydrogen bond acceptors and hydrophobic group being arranged so that when the inhibitor binds to MMP-13:

the first, second and third hydrogen bond acceptors bond respectively with backbone NH's of Thr245, Thr 247 and Met 253; and

the first hydrophobic group locates within the S1' channel.

8. A combination, comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13 that comprises

a monocyclic, bicyclic, or tricyclic scaffold, wherein the bicyclic scaffold comprises a first ring fused to a second ring and the tricyclic scaffold comprises a first ring fused to a second ring, which is in turn fused to a third ring;

first, second and third hydrogen bond acceptors, and

first and second hydrophobic groups connected by linker chains to the scaffold, a cyclic structure forming part of the scaffold being located between the first and second hydrogen bond acceptors, and the hydrogen bond acceptors and hydrophobic groups being arranged so that when the inhibitor binds to MMP-13:

the first, second and third hydrogen bond acceptors bond respectively with the backbone NH's of Thr245, Thr 247 and Met 253;

the first hydrophobic group locates within the S1' channel; and

the second hydrophobic group is open to solvent.

9. The combination of Embodiment 8, wherein the third hydrogen bond acceptor may additionally form a hydrogen bond via a bridging water molecule with the backbone carbonyl of His251.

10. The combination of any one of Embodiments 6, 7, 8, and 9, wherein the scaffold is a phenylene or a 5-membered or 6-membered monocyclic heteroaromatic ring diradical containing carbon atoms and from 1 to 4 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the scaffold is unsubstituted or substituted with 1 or 2 groups selected from: halo, methyl, and methoxy.

11. The combination of any one of Embodiments 6, 7, 8, and 9, wherein the scaffold is a fused bicyclic ring diradical, wherein a first ring is fused to a second ring, selected from: naphthalene and an 8-membered to 10-membered fused heteroaromatic bicyclic ring containing carbon atoms and optionally from 1 to 4 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein at least one ring of the fused bicyclic ring is phenylene or a 5-membered or 6-membered heteroaromatic ring containing carbon atoms and from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the scaffold is unsubstituted or substituted with from 1 to 3 groups selected from: halo, methyl, and methoxy.

12. The combination of Embodiment 11, wherein at least one ring is a phenylene.

13. The combination of any one of Embodiments 6, 7, 8, and 9, wherein the scaffold is a bis-fused tricyclic ring diradical, wherein a first ring is fused to a second ring, which is fused to a third ring, selected from:

a bis-fused 14-membered aromatic tricyclic ring diradical of molecular formula $C_{14}H_8$; and

a bis-fused 10-membered to 14-membered heteroaromatic tricyclic ring diradical containing carbon atoms and from 1 to 6 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein at least one ring of the bis-fused heteroaromatic tricyclic ring diradical is a phenylene or a 5-membered or 6-membered heteroaromatic ring containing carbon atoms and from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the scaffold is unsubstituted or substituted with from 1 to 5 groups selected from: halo, methyl, and methoxy.

14. The combination of any one of Embodiments 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13, wherein the hydrophobic group, or when two hydrophobic groups are present, the first hydrophobic group, is

C_4-C_{10} n-alkyl;

C_4-C_{10} n-alkenyl;

C_4-C_{10} n-alkynyl, wherein the C_4-C_{10} n-alkyl, C_4-C_{10} n-alkenyl, and C_4-C_{10} n-alkynyl optionally contain an O or S in place of a carbon atom,

8-membered to 10-membered fused bicyclic ring containing carbon atoms and optionally from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl;

5-membered or 6-membered cycloalkyl;

5-membered or 6-membered heterocycloalkyl containing carbon atoms and optionally from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl;

phenyl; or

5-membered or 6-membered heteroaryl containing carbon atoms and optionally from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl,

wherein the 6-membered cycloalkyl, 6-membered heterocycloalkyl, phenyl, or 6-membered heteroaryl are unsubstituted or monosubstituted in the 4-position or disubstituted in the 3-position and 4-position, wherein the substituents are selected from C_1-C_4 alkyl, OH, O-(C_1-C_4 alkyl), SH, S-(C_1-C_4 alkyl), and NR_aR_b, wherein R_a and R_b are each independently selected from H and C_1-C_4 alkyl, and the width of the substituted 6-membered cycloalkyl, 6-membered heterocycloalkyl, phenyl, or 6-membered heteroaryl is less than 4.0 Å.

15. The combination of Embodiment 14, wherein the hydrophobic group is phenyl or 6-membered heteroaryl.

16. The combination of Embodiment 14, wherein the hydrophobic group is 6-membered heteroaryl.

17. The combination of any one of Embodiments 10, 11, 12, and 13, wherein the hydrophobic group, or where there are two such groups the first hydrophobic group, is linked to the scaffold by a first linker chain containing from 1 to 3 atoms selected from carbon atoms and optionally 1 or 2 heteroatoms, wherein the heteroatoms are selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl.

18. The combination of Embodiment 17, wherein the chain contains 3 carbon atoms.

19. The combination of Embodiment 18, wherein the carbon atom of the chain bonded to the hydrophobic group, or where there are two such groups the first hydrophobic group, is a CH_2.

20. The combination of any one of Embodiments 3, 5, 6, 8, and 9, wherein the second hydrophobic group is

8-membered to 10-membered fused bicyclic ring containing carbon atoms and optionally from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl;

5-membered or 6-membered cycloalkyl;

5-membered or 6-membered heterocycloalkyl containing carbon atoms and optionally from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl;

phenyl; or

5-membered or 6-membered heteroaryl containing carbon atoms and optionally from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl,

wherein the 6-membered cycloalkyl, 6-membered heterocycloalkyl, phenyl, or 6-membered heteroaryl are unsubstituted or monosubstituted in the 4-position or disubstituted in the 3-position and 4-position, wherein the substituents are selected from C_1-C_4 alkyl, OH, O-(C_1-C_4 alkyl), SH, S-(C_1-C_4 alkyl), and NR_aR_b, wherein R_a and R_b are each independently selected from H and C_1-C_4 alkyl, and the width of the substituted 6-membered cycloalkyl, 6-membered heterocycloalkyl, phenyl, or 6-membered heteroaryl is less than 4.0 Å.

21. The combination of Embodiment 20, wherein the second hydrophobic group is phenyl, 5-membered heteroaryl, or 6-membered heteroaryl.

22. The combination of any one of Embodiments 6, 8, and 9, wherein the second hydrophobic group is linked to the scaffold by a second linker chain containing from 1 to 3 atoms selected from carbon atoms and optionally 1 or 2 heteroatoms, wherein the heteroatoms are selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl.

23. The combination of Embodiment 22, wherein the scaffold is a phenylene or a 5-membered or 6-membered monocyclic heteroaromatic ring diradical

containing carbon atoms and from 1 to 4 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the scaffold is unsubstituted or substituted with 1 or 2 groups selected from: halo, methyl, and methoxy and the second linker chain contains 3 atoms.

24. The combination of Embodiment 23, wherein the second linker chain atom bonded to the scaffold comprises the second hydrogen bond acceptor.

25. The combination of Embodiment 22, wherein the scaffold is

a fused bicyclic ring diradical, wherein a first ring is fused to a second ring, selected from: naphthalene and an 8-membered to 10-membered fused heteroaromatic bicyclic ring containing carbon atoms and optionally from 1 to 4 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein at least one ring of the fused bicyclic ring is phenylene or a 5-membered or 6-membered heteroaromatic ring containing carbon atoms and from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the scaffold is unsubstituted or substituted with from 1 to 3 groups selected from: halo, methyl, and methoxy; or

a bis-fused tricyclic ring diradical, wherein a first ring is fused to a second ring, which is fused to a third ring, selected from: bis-fused 14-membered aromatic tricyclic ring diradical of molecular formula $C_{14}H_8$ and a bis-fused 10-membered to 14-membered heteroaromatic tricyclic ring diradical containing carbon atoms and from 1 to 6 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein at least one ring of the bis-fused heteroaromatic tricyclic ring diradical is a phenylene or a 5-membered or 6-membered heteroaromatic ring containing carbon atoms and from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the scaffold is unsubstituted or substituted with from 1 to 5 groups selected from: halo, methyl, and methoxy; and

the second hydrophobic group is linked to the scaffold by a second linker chain which is CH_2.

26. The combination of any one of Embodiments 6, 8, and 9, wherein the second hydrophobic group is linked to the scaffold by a second linker chain containing from 1 to 3 atoms selected from carbon atoms and optionally 1 or 2 heteroatoms, wherein the heteroatoms are selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl.

27. The combination of any one of Embodiments 6, 8, and 9, wherein the first hydrophobic group is linked through a first linker chain to the scaffold and the scaffold is linked through a second linker chain to the second hydrophobic group, wherein the bonds from the first and second linker chains are to different atoms of the monocyclic scaffold or different atoms of the first ring of the bicyclic scaffold or different atoms of the first ring of the tricyclic scaffold, and further wherein the scaffold atoms bonded to the linker chains are separated from each other by from 1 to 3 atoms.

28. The combination of Embodiment 27, wherein the scaffold atoms that are bonded to the linker chains are separated from each other by one atom.

29. The combination of Embodiment 27, wherein the first and second linker chains are bonded to the scaffold at atoms in the chains which comprise the first and second hydrogen bond acceptors, respectively.

30. The combination of Embodiment 27, wherein the scaffold is substituted with a substituent that is para to the junction of the first linker chain with the ring, wherein the substituent is selected from halo, C_1-C_4 alkyl, OH, O-(C_1-C_4 alkyl), SH, S-(C_1-C_4 alkyl), and NR_aR_b, wherein R_a and R_b are each independently selected from H and C_1-C_4 alkyl.

31. The combination of Embodiment 30, wherein the substituent is methyl or methoxy.

32. The combination of Embodiment 27, wherein the scaffold is the bicyclic scaffold wherein the second ring is fused to the first ring at first and second atom junctions, and the first and second atom junctions are bonded to first and second nonjunction atoms of the second ring, respectively, wherein

the first atom junction is two atoms distance from the atom of the first ring which is bonded to the first linker chain, wherein the two atoms are unsubstituted or substituted with fluoro; and

the second nonjunction atom of the second ring is unsubstituted or substituted with halo or methyl.

33. The combination of Embodiment 32, wherein the two atoms are unsubstituted.

34. The combination of Embodiments 32 or 33, wherein the first nonjunction atom of the second ring comprises the second hydrogen bond acceptor.

35. The combination of any one of Embodiments 32, 33, and 34, wherein the second nonjunction atom of the second ring is substituted with halo or methyl.

36. The combination of any one of Embodiments 32, 33, 34, and 35, wherein the second ring is a 6-membered ring.

37. The combination of Embodiment 36, wherein another nonjunction atom of the second ring that is separated by one ring atom from the first nonjunction atom of the second ring, comprises a third hydrogen bond acceptor.

38. The combination of Embodiment 27, wherein the scaffold is a tricyclic scaffold wherein the second ring is fused to the first ring at first and second atom junctions, and the third ring is fused to the second ring at third and fourth atom junctions, wherein the third atom junction is a second two atoms distance from the first nonjunction atom of the second ring.

39. The combination of Embodiment 38, wherein the second ring is a 6-membered ring.

40. The combination of Embodiment 38 or 39, wherein a nonjunction atom of the third ring comprises the third hydrogen bond acceptor.

41. The combination according to any one of Embodiments 2 to 40, wherein the molecular weight of the allosteric inhibitor of MMP-13 is less than 1001.

42. The combination according to any one of Embodiments 2 to 41, wherein the molecular weight of the allosteric inhibitor of MMP-13 is less than 751.

43. The combination according to any one of Embodiments 2 to 42, wherein the molecular weight of the allosteric inhibitor of MMP-13 is less than 601.

44. The combination according to any one of Embodiments 2 to 43, wherein the molecular weight of the allosteric inhibitor of MMP-13 is less than 551.

45. The combination according to any one of Embodiments 2 to 44, wherein the molecular weight of the allosteric inhibitor of MMP-13 is less than 501.

46. A pharmaceutical composition, comprising a combination of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

47. The pharmaceutical composition according to Embodiment 46, wherein the combination is the combination according to any one of Embodiments 2 to 45.

48. The pharmaceutical composition according to Embodiment 46 or 47, wherein the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 1 milligram to 500 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 600 milligrams.

49. The pharmaceutical composition according to Embodiment 48, wherein the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 2 milligrams to 250 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 300 milligrams.

50. The pharmaceutical composition according to Embodiment 49, wherein the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 300 milligrams.

51. The pharmaceutical composition according to Embodiment 50, wherein the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 200 milligrams.

52. The pharmaceutical composition according to Embodiment 51, wherein the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligram to 100 milligrams, and the

allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 100 milligrams.

53. A method of treating cartilage damage in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

54. The method according to Embodiment 53, wherein the combination is the combination according to any one of Embodiments 2 to 45.

55. A method of treating cartilage damage in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition, comprising a combination of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

56. The method according to Embodiment 55, wherein the combination is the combination according to any one of Embodiments 2 to 45.

57. The method according to Embodiment 55 or 56, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 1 milligram to 500 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 600 milligrams.

58. The method according to Embodiment 57, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 2 milligrams to 250 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 300 milligrams.

59. The method according to Embodiment 58, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor

of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 300 milligrams.

60. The method according to Embodiment 59, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 200 milligrams.

61. The method according to Embodiment 60, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligram to 100 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 100 milligrams.

61. A method of treating inflammation in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

62. The method according to Embodiment 61, wherein the combination is the combination according to any one of Embodiments 2 to 45.

63. A method of treating inflammation in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition, comprising a combination of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

64. The method according to Embodiment 63, wherein the combination is the combination according to any one of Embodiments 2 to 45.

65. The method according to Embodiment 63 or 64, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 1 milligram to 500 milligrams, and the

allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 600 milligrams.

66. The method according to Embodiment 65, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 2 milligrams to 250 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 300 milligrams.

67. The method according to Embodiment 66, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 300 milligrams.

68. The method according to Embodiment 67, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 200 milligrams.

69. The method according to Embodiment 68, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligram to 100 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 100 milligrams.

70. A method of treating osteoarthritis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

71. The method according to Embodiment 70, wherein the combination is the combination according to any one of Embodiments 2 to 45.

72. A method of treating osteoarthritis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition, comprising a combination of a selective inhibitor of

COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

73. The method according to Embodiment 72, wherein the combination is the combination according to any one of Embodiments 2 to 45.

74. The method according to Embodiment 72 or 73, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 1 milligram to 500 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 600 milligrams.

75. The method according to Embodiment 74, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 2 milligrams to 250 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 300 milligrams.

76. The method according to Embodiment 75, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 300 milligrams.

77. The method according to Embodiment 76, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 200 milligrams.

78. The method according to Embodiment 77, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligram to 100 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 100 milligrams.

79. A method of treating rheumatoid arthritis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

80. The method according to Embodiment 79, wherein the combination is the combination according to any one of Embodiments 2 to 45.

81. A method of treating rheumatoid arthritis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition, comprising a combination of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

82. The method according to Embodiment 83, wherein the combination is the combination according to any one of Embodiments 2 to 45.

83. The method according to Embodiment 81 or 82, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 1 milligram to 500 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 600 milligrams.

84. The method according to Embodiment 83, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 2 milligrams to 250 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 300 milligrams.

85. The method according to Embodiment 84, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 300 milligrams.

86. The method according to Embodiment 85, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 200 milligrams.

87. The method according to Embodiment 86, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligram to 100 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 100 milligrams.

88. A method of treating psoriatic arthritis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

89. The method according to Embodiment 88, wherein the combination is the combination according to any one of Embodiments 2 to 45.

90. A method of treating psoriatic arthritis in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition, comprising a combination of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

91. The method according to Embodiment 90, wherein the combination is the combination according to any one of Embodiments 2 to 45.

92. The method according to Embodiment 90 or 91, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 1 milligram to 500 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 600 milligrams.

93. The method according to Embodiment 92, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 2 milligrams to 250 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 300 milligrams.

94. The method according to Embodiment 93, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 300 milligrams.

95. The method according to Embodiment 94, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 200 milligrams.

96. The method according to Embodiment 95, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligram to 100 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 100 milligrams.

97. A method of treating pain in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

98. The method according to Embodiment 97, wherein the combination is the combination according to any one of Embodiments 2 to 45.

99. A method of treating pain in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of a pharmaceutical composition, comprising a combination of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically

acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

100. The method according to Embodiment 99, wherein the combination is the combination according to any one of Embodiments 2 to 45.

101. The method according to Embodiment 99 or 100, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 1 milligram to 500 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 600 milligrams.

102. The method according to Embodiment 101, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 2 milligrams to 250 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 10 milligrams to 300 milligrams.

103. The method according to Embodiment 102, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 300 milligrams.

104. The method according to Embodiment 103, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligrams to 200 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 200 milligrams.

105. The method according to Embodiment 104, wherein the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 5 milligram to 100 milligrams, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is in unit dosage form in an amount of from 25 milligrams to 100 milligrams.

Another invention embodiment is any of the above embodiments of a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single

compound named below in the Examples of allosteric inhibitors of MMP-13, with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

Another invention embodiment is any of the above embodiments of pharmaceutical compositions, comprising a combination containing an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, together with a pharmaceutically acceptable carrier, diluent, or excipient.

Another invention embodiment is any of the above embodiments of a methods of treating a disease in a mammal suffering therefrom, comprising administering to the mammal a therapeutically effective amount of a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

Another invention embodiment is a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

Another invention embodiment is a pharmaceutical composition, comprising a combination containing an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, together with a pharmaceutically acceptable carrier, diluent, or excipient.

Another invention embodiment is a method of treating a disease that is responsive to inhibition of MMP-13 and to selective inhibition of COX-2 in a

mammal suffering therefrom, comprising administering to the mammal a therapeutically effective amount of the combination according to any one of Embodiments 1 to 45.

Another invention embodiment is a method of treating a disease that is responsive to inhibition of MMP-13 and to selective inhibition of COX-2 in a mammal suffering therefrom, comprising administering to the mammal a therapeutically effective amount of a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

Another invention embodiment is a method of treating a first disease that is responsive to inhibition of MMP-13 and a second disease that is responsive to selective inhibition of COX-2 in a mammal suffering therefrom, comprising administering to the mammal a therapeutically effective amount of the combination according to any one of Embodiments 1 to 45.

Another invention embodiment is a method of treating a first disease that is responsive to inhibition of MMP-13 and a second disease that is responsive to selective inhibition of COX-2 in a mammal suffering therefrom, comprising administering to the mammal a therapeutically effective amount of a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

Another embodiment of the invention is a combination comprising an NSAID, or a pharmaceutically acceptable salt thereof, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof.

Another invention embodiment is a combination according to any one of Embodiments 1 to 45, except where the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is replaced by an NSAID, or a pharmaceutically acceptable salt thereof.

Another invention embodiment is a combination according to any one of Embodiments 1 to 45, except where the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is replaced by an NSAID, or a pharmaceutically acceptable salt thereof, and wherein the NSAID is selected from:

Naproxen;
Naproxen sodium;
Ibuprofen;
Acetominophen;
Aspirin;
Sulindac;
Tolmetin;
Piroxicam;
Mefenamic acid;
Phenylbutazone;
Fenoprofen;
Ketoprofen;
Suprofen;
Diflunisal; and
meloxicam.

Another invention embodiment is a combination according to any one of Embodiments 1 to 45, except where the selective inhibitor of COX-2, or the pharmaceutically acceptable salt thereof, is replaced by an NSAID, or a pharmaceutically acceptable salt thereof, and wherein the NSAID is selected from:

Naproxen;
Naproxen sodium;
Ibuprofen;
Acetominophen; and
Aspirin.

Another invention embodiment is a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the

allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with an NSAID, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a pharmaceutical composition, comprising a combination of an NSAID, or a pharmaceutically acceptable salt thereof, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier, diluent, or excipient.

Another invention embodiment is a pharmaceutical composition, comprising a combination containing an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with an NSAID, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier, diluent, or excipient.

Another invention embodiment is a method of treating a disease that is responsive to inhibition of MMP-13 and to inhibition of COX-1 or COX-2 in a mammal suffering therefrom, comprising administering to the mammal a therapeutically effective amount of a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with an NSAID, or a pharmaceutically acceptable salt thereof.

Another invention embodiment is a method of treating a first disease that is responsive to inhibition of MMP-13 and a second disease that is responsive to inhibition of COX-1 or COX-2 in a mammal suffering therefrom, comprising administering to the mammal a therapeutically effective amount of the combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with an NSAID, or a pharmaceutically acceptable salt thereof.

Another invention embodiment is a method of treating a first disease that is responsive to inhibition of MMP-13 and a second disease that is responsive to

inhibition of COX-1 or COX-2 in a mammal suffering therefrom, comprising administering to the mammal a therapeutically effective amount of a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, wherein the allosteric inhibitor of MMP-13 is any single compound named below in the Examples of allosteric inhibitors of MMP-13, with an NSAID, or a pharmaceutically acceptable salt thereof.

Another invention embodiment is a method of treating an arthritic condition in a mammal, comprising administering to the mammal an amount of any one of the above described invention combinations, or any one of the above-described invention pharmaceutical compositions, sufficient to effectively treat the arthritic condition.

Use of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating cartilage damage in a mammal in need thereof.

Use of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating inflammation in a mammal in need thereof.

Use of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating osteoarthritis in a mammal in need thereof.

Use of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating rheumatoid arthritis in a mammal in need thereof.

Use of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating psoriatic arthritis in a mammal in need thereof.

Use of a combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for treating pain in a mammal in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the invention provides a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib. This invention also provides a method of treating a disease that is responsive to inhibition of MMP-13 and cyclooxygenase-2, comprising administering to a patient suffering from such a disease the invention combination comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib. This invention also provides a pharmaceutical composition, comprising the invention combination comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and a pharmaceutically acceptable carrier, diluent, or excipient.

The invention further provides a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with an NSAID, or a pharmaceutically acceptable salt thereof. This invention also provides a method of treating a disease that is responsive to inhibition of MMP-13 and cyclooxygenase-1 or cyclooxygenase-2, comprising administering to a patient

suffering from such a disease the invention combination comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with an NSAID, or a pharmaceutically acceptable salt thereof. This invention also provides a pharmaceutical composition, comprising the invention combination comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with an NSAID, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

The invention combinations may also be further combined with other pharmaceutical agents depending on the disease being treated.

The terms are as defined below or as they otherwise occur in the specification.

The term "pharmacophore" means the minimum functionality of a compound required to exhibit activity and is commonly defined in terms of affinity characteristics between a center or centers and an enzyme or receptor target. One way of defining the pharmacophore is by the description of the necessary centers and their relative positions in space in combination with their receptor or enzyme affinity characteristics.

As mentioned previously, the main features of the instant pharmacophore may broadly comprise a first hydrophobic group, and optionally a second hydrophobic group, and first and second hydrogen bond acceptors, and optionally a third hydrogen bond acceptor, connected by linker chains to a scaffold. The scaffold is preferably, but not necessarily, a cyclic group. In any event, the scaffold is any group which serves to orient the first hydrophobic group, and optionally a second hydrophobic group, and the first and second hydrogen bond acceptors, and optionally the third hydrogen bond acceptor, and the linker chains, to allow affinity interactions between the compound containing the pharmacophore and the enzyme or receptor binding target. These main features have been described above in detail and exemplified below.

For the purposes of the instant invention, an allosteric inhibitor of MMP-13 is any compound with a molecular weight under 2001 atomic units which satisfies the binding criteria described above for any one of invention Embodiments 2 to 45.

More particularly, an allosteric inhibitor of MMP-13 is any compound that binds allosterically into the S1' site of the enzyme, including the S1' channel, and a newly discovered S1" site, without ligating the catalytic zinc of MMP-13.

It should be appreciated that the S1' site of MMP-13 was a grossly linear channel which contained an opening at the top that allowed an amino acid side chain from a substrate to enter during binding, and was closed at the bottom. Applicant has discovered that the S1' site is actually composed of an S1' channel angularly connected to a newly discovered pocket which applicant calls the S1" site. The S1" site is open to solvent at the bottom, which can expose a functional group of Applicant's allosteric inhibitors to solvent. For illustrative purposes, the S1' site of the MMP-13 enzyme can now be thought of as being like a sock with a hole in the toes, wherein the S1' channel is the region from approximately the opening to the ankle, and the S1" site is the foot region below the ankle.

More particularly, the S1' channel is a specific part of the S1' site and is formed largely by Leu218, Val219, His222 and by residues from Leu239 to Tyr244. The S1" binding site which has been newly discovered is defined by residues from Tyr246 to Pro255. The S1" site contains at least two hydrogen bond donors and aromatic groups which interact with a compound which is an allosteric inhibitor of MMP-13.

Without wishing to be bound by any particular theory, the inventor believes that the S1" site could be a recognition site for triple helix collagen, the natural substrate for MMP-13. It is possible that the conformation of the S1" site is modified only when an appropriate compound binds to MMP-13, thereby interfering with the collagen recognition process. This newly discovered pattern of binding offers the possibility of greater selectivity than what is achievable with the binding pattern of known selective inhibitors of MMP-13, wherein the known binding pattern requires ligation of the catalytic zinc atom at the active site and occupation the S1' channel, but not the S1" site.

The invention provides compounds that bind allosterically to and inhibit MMP-13 and that have a pharmacophore comprising at least a first hydrophobic group and at least first and second hydrogen bond acceptors. The compound will

normally have a second hydrophobic group, a third hydrogen bond acceptor or both a second hydrophobic group and a third hydrogen bond acceptor.

The second hydrophobic group when present can contribute significantly to selectivity because it has been found to stabilize and interact with the S1" site of the MMP enzyme.

A further way of defining the pharmacophore is in terms of the centers present and the sites on the receptor with which they interact.

The existence and properties of the pharmacophore described above are supported by:

(i) crystal structure determinations of matrix metalloproteinase-13 catalytic domain ("MMP-13 catalytic domain" or "MMP-13CD") having inhibitors according to the invention bonded thereto, which structure determinations have provided detailed information concerning the sites which are important for allosteric binding between a inhibitor and MMP-13CD; and

(ii) structure-activity relationships that have previously determined allosteric MMP-13 inhibitor compounds within a number of series. Some of these compounds are described in co-pending PCT international applications which claim the benefit of priority from United States provisional application numbers 60/268,780; 60/268,736; 60/268,756; 60/268,821; 60/268,861; 60/268,757; 60/268,782; 60/268,779; and 60/268,781, all filed on February 14, 2001. United States nonprovisional application numbers 10/071,032; 10/075,918; 10/075,073; 10/075,069; 10/075,954; 10/075,654; 10/074,646; 10/075,909; and 10/071,073 related to the PCT international applications referenced above have also been filed and claim benefit of priority from United States provisional application numbers 60/268,780; 60/268,736; 60/268,756; 60/268,821; 60/268,661; 60/268,757; 60/268,782; 60/268,779; and 60/268,781, respectively. Other compounds are described in United States provisional application number 60/329,216; and United States provisional application number 60/329,181, which is related to co-pending PCT international application PCT/EP01/11824, all filed on October 12, 2001. All of these United States provisional applications, United States nonprovisional applications, and PCT international applications are incorporated herein by

reference. For convenience, the allosteric inhibitors of MMP-13 patent application filing information is listed below in Table A.

Table A: Allosteric inhibitors of MMP-13 patent application filing information

U.S. Provisional Application Number	U.S. Provisional Application Filing Date	Corresponding U.S. Nonprovisional Application Number	Corresponding PCT International Application Number
60/268,780	February 14, 2001	10/071,032	PCT/IB02/00313
60/268,736	February 14, 2001	10/075,918	PCT/IB02/00344
60/268,756	February 14, 2001	10/075,073	PCT/IB02/00204
60/268,821	February 14, 2001	10/075,069	PCT/IB02/00447
60/268,661	February 14, 2001	10/075,954	PCT/EP02/01979
60/268,757	February 14, 2001	10/075,654	PCT/FR02/00504
60/268,782	February 14, 2001	10/074,646	PCT/IB02/00083
60/268,779	February 14, 2001	10/075,909	PCT/IB02/00190
60/268,781	February 14, 2001	10/071,073	PCT/IB02/00345
60/329,216	October 12, 2001	NF[a]	NF
60/329,181	October 12, 2001	NF	PCT/EP01/11824

(a) NF means application not filed

A compound that is an allosteric inhibitor of MMP-13 may be readily identified by one of ordinary skill in the pharmaceutical or medical arts by assaying a test compound for inhibition of MMP-13 as described below in Biological Methods 1 or 2, and for allosteric inhibition of MMP-13 by assaying the test compound for inhibition of MMP-13 in the presence of an inhibitor to the catalytic zinc of MMP-13 as described below in Biological Methods 3 or 4.

Further, an allosteric inhibitor of MMP-13 having an anti-inflammatory, an analgesic, anti-arthritic, or a cartilage damage inhibiting effect, or any combination of these effects, may be readily identified by one of ordinary skill in the pharmaceutical or medical arts by assaying the allosteric inhibitor of MMP-13

in any number of well known assays for measuring determining the allosteric inhibitor of MMP-13's effects on cartilage damage, arthritis, inflammation, or pain. These assays include in vitro assays that utilize cartilage samples and in vivo assays in whole animals that measure cartilage degradation, inhibition of inflammation, or pain alleviation.

For example with regard to assaying cartilage damage in vitro, an amount of an allosteric inhibitor of MMP-13 or control vehicle may be administered with a cartilage damaging agent to cartilage, and the cartilage damage inhibiting effects in both tests studied by gross examination or histopathologic examination of the cartilage, or by measurement of biological markers of cartilage damage such as, for example, proteoglycan content or hydroxyproline content. Further, in vivo assays to assay cartilage damage may be performed as follows: an amount of an allosteric inhibitor of MMP-13 or control vehicle may be administered with a cartilage damaging agent to an animal, and the effects of the allosteric inhibitor of MMP-13 being assayed on cartilage in the animal may be evaluated by gross examination or histopathologic examination of the cartilage, by observation of the effects in an acute model on functional limitations of the affected joint that result from cartilage damage, or by measurement of biological markers of cartilage damage such as, for example, proteoglycan content or hydroxyproline content.

Several methods of identifying an allosteric inhibitor of MMP-13 with cartilage damage inhibiting properties are described below. The amount to be administered in an assay to identify an allosteric inhibitor of MMP-13 is dependent upon the particular assay employed, but in any event is not higher than the well known maximum amount of a compound that the particular assay can effectively accommodate.

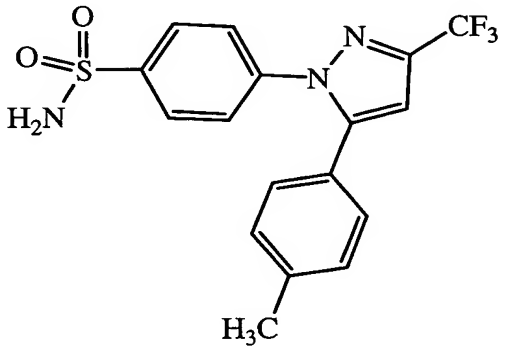
Similarly, allosteric inhibitors of MMP-13 having pain-alleviating properties may be identified using any one of a number of in vivo animal models of pain.

Still similarly, allosteric inhibitors of MMP-13 having anti-inflammatory properties may be identified using any one of a number of in vivo animal models of inflammation. For example, for an example of inflammation models, see United States patent number 6, 329,429, which is incorporated herein by reference.

Still similarly, allosteric inhibitors of MMP-13 having anti-arthritic properties may be identified using any one of a number of in vivo animal models of arthritis. For example, for an example of arthritis models, see also United States patent number 6, 329,429.

Any allosteric inhibitor of MMP-13 is readily available, either commercially, or by synthetic methodology, well known to those skilled in the art of organic chemistry. For specific syntheses, see the examples below and the preparations of allosteric inhibitors of MMP-13 described in the above-referenced patent applications.

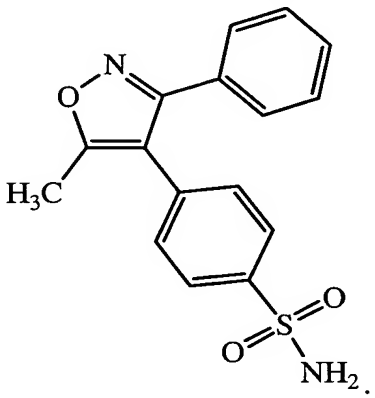
The term "celecoxib" means the compound named 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-benzenesulfonamide, or a pharmaceutically acceptable salt thereof. Celecoxib which is named 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-benzenesulfonamide is currently approved by the FDA for the treatment of osteoarthritis, rheumatoid arthritis, and Polyposis-familial adenomatus. The approved celecoxib is marketed under the tradename "Celebrex". Celecoxib is currently in clinical trials for the treatment of bladder cancer, chemopreventative-lung cancer, and post-operative pain, and is registered for the treatment of dysmenorrhea. Celecoxib which is named 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-benzenesulfonamide has the structure drawn below:



It should be appreciated that no invention combination may include celecoxib, or a pharmaceutically acceptable salt thereof, even if the invention combination is inadvertently defined otherwise herein.

The term "valdecoxib" means the compound named 4-(5-methyl-3-phenyl-4-isoxazolyl)-benzenesulfonamide, or a pharmaceutically acceptable salt thereof.

Valdecoxib which is named 4-(5-methyl-3-phenyl-4-isoxazolyl)-benzenesulfonamide has been approved by the FDA for treating osteoarthritis, rheumatoid arthritis, dysmenorrhea, and general pain, and is marketed under the tradename "Bextra". Valdecoxib is in clinical trials for the treatment of migraine. Valdecoxib has the structure drawn below:



It should be appreciated that no invention combination may include valdecoxib, or a pharmaceutically acceptable salt thereof, even if the invention combination is inadvertently defined otherwise herein.

It should be further appreciated that the enzyme COX-2 is also known as prostaglandin synthase-2 and prostaglandin PGH_2 synthase.

A selective inhibitor of COX-2 means compounds that inhibit COX-2 selectively versus COX-1 such that a ratio of IC_{50} for a compound with COX-1 divided by a ratio of IC_{50} for the compound with COX-2 is greater than, or equal to, 5, where the ratios are determined in one or more of the in vitro, in vivo, or ex vivo assays described below. All that is required to determine whether a compound is a selective COX-2 inhibitor is to assay a compound in one of the pairs of assays described in Biological Methods 5 to 8 below. Preferred selective COX-2 inhibitors have a selectivity greater than 5 fold versus COX-1 in the assay described in Biological Method 5 below.

For the purposes of this invention, a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib includes a compound, or a pharmaceutically acceptable salt thereof, selected from:

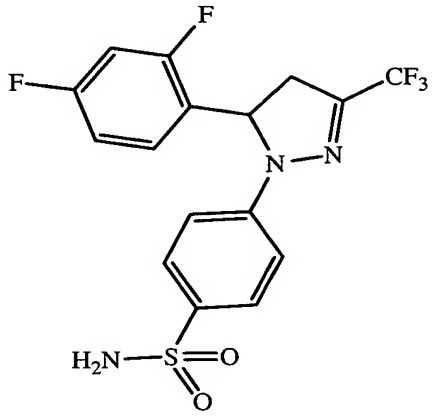
ABT-963;

Valdecoxib;

BMS-347070;

Tilacoxib;

The compound of formula (B)



(B)

;

CS-502 [Chemical Abstracts Service Registry Number ("CAS Reg. No.") 176429-82-6];

(6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid ("CT-3");

CV-247;

2(5H)-Furanone, 5,5-dimethyl-3-(1-methylethoxy)-4-[4-(methylsulfonyl)phenyl]- ("DFP");

DuP-697;

Etoricoxib;

Lumiracoxib (tradename "PREXIGE");

GW-406381;

Tiracoxib;

Meloxicam;

Nimesulide;

2-(Acetyloxy)benzoic acid, 3-[(nitrooxy)methyl]phenyl ester ("NCX-4016");

Parecoxib;

P54 (CAS Reg. No. 130996-28-0);

Rofecoxib;

RevlMiD;

2,6-Bis(1,1-dimethylethyl)-4-[(E)-(2-ethyl-1,1-dioxo-5-isothiazolidinylidene)methyl]phenol ("S-2474");

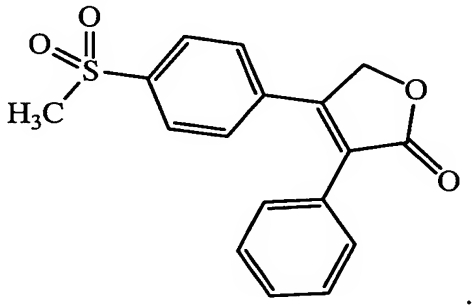
5(R)-Thio-6-sulfonamide-3(2H)-benzofuranone ("SVT-2016"); and

N-[3-(Formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide ("T-614"), or a pharmaceutically acceptable salt thereof.

The term "etoricoxib" means the compound marketed in the United Kingdom under the tradename "Arcoxia". Arcoxia has been approved in the United Kingdom as a once-daily medicine for symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis, acute gouty arthritis, relief of chronic musculo-skeletal pain, including chronic low back pain, relief of acute pain associated with dental surgery, and treatment of primary dysmenorrhea.

It should be appreciated that an invention combination may include etoricoxib, or a pharmaceutically acceptable salt thereof.

The term "rofecoxib" means the compound named 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone. Rofecoxib has been approved by the FDA for treatment of osteoarthritis, general pain, and post-operative pain, and is preregistered for treatment of rheumatoid arthritis. Rofecoxib is marketed under the tradename "Vioxx". Rofecoxib is currently in clinical trials for treatment of juvenile rheumatoid arthritis, colorectal cancer, colorectal cancer prevention, polyposis-familial adenomatus ("FAP"), and polyposis-spontaneous adenomatous-prevention. Rofecoxib has the structure drawn below:



It should be appreciated that the invention combination may include rofecoxib, or a pharmaceutically acceptable salt thereof.

The term "NSAID" is an acronym for the phrase "nonsteroidal anti-inflammatory drug", which means any compound which inhibits cyclooxygenase-

1 ("COX-1") and cyclooxygenase-2. Most NSAIDs fall within one of the following five structural classes: (1) propionic acid derivatives, such as ibuprofen, naproxen, naprosyn, diclofenac, and ketoprofen; (2) acetic acid derivatives, such as tolmetin and sulindac; (3) fenamic acid derivatives, such as mefenamic acid and meclofenamic acid; (4) biphenylcarboxylic acid derivatives, such as diflunisal and flufenisal; and (5) oxicams, such as piroxim, peroxicam, sudoxicam, and isoxicam. Other useful NSAIDs include aspirin, acetominophen, indomethacin, and phenylbutazone. Selective inhibitors of cyclooxygenase-2 as described above may be considered to be NSAIDs also. However, for the present purposes, an NSAID which is celecoxib or valdecoxib is excluded from any invention embodiment.

For the purposes of this invention, the term "arthritis", which is synonymous with the phrase "arthritic condition", includes osteoarthritis, rheumatoid arthritis, degenerative joint disease, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, and psoriatic arthritis. An allosteric inhibitor of MMP-13 having an anti-arthritic effect is a compound as defined above that inhibits the progress, prevents further progress, or reverses progression, in part or in whole, of any one or more symptoms of any one of the arthritic diseases and disorders listed above.

Other mammalian diseases and disorders which are treatable by administration of an invention combination alone, or contained in a pharmaceutical composition as defined below, include: fever (including rheumatic fever and fever associated with influenza and other viral infections), common cold, dysmenorrhea, menstrual cramps, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer; hematopoietic malignancies including leukemias and lymphomas; Hodgkin's disease; aplastic anemia, skin cancer and familiar adenomatous polyposis), tissue ulceration, peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, recurrent gastrointestinal lesion, gastrointestinal bleeding,

coagulation, anemia, synovitis, gout, ankylosing spondylitis, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, atherosclerosis (including atherosclerotic plaque rupture), aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), periarteritis nodosa, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, spinal cord injury, neuralgia, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain (including low back and neck pain, headache and toothache), gingivitis, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, conjunctivitis, abnormal wound healing, muscle or joint sprains or strains, tendonitis, skin disorders (such as psoriasis, eczema, scleroderma and dermatitis), myasthenia gravis, polymyositis, myositis, bursitis, burns, diabetes (including types I and II diabetes, diabetic retinopathy, neuropathy and nephropathy), tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, immunodeficiency diseases (such as AIDS in humans and FLV, FIV in cats), sepsis, premature labor, hypoprothrombinemia, hemophilia, thyroiditis, sarcoidosis, Behcet's syndrome, hypersensitivity, kidney disease, Rickettsial infections (such as Lyme disease, Erlichiosis), Protozoan diseases (such as malaria, giardia, coccidia), reproductive disorders (preferably in livestock), epilepsy, convulsions, and septic shock.

It should be appreciated that the matrix metalloproteinases include, but are not limited to, the following enzymes:

MMP-1, also known as interstitial collagenase, collagenase-1, or fibroblast-type collagenase;

MMP-2, also known as gelatinase A or 72 kDa Type IV collagenase;

MMP-3, also known as stromelysin or stromelysin-1;

MMP-7, also known as matrilysin or PUMP-1;

MMP-8, also known as collagenase-2, neutrophil collagenase or polymorphonuclear-type ("PMN-type") collagenase;

MMP-9, also known as gelatinase B or 92 kDa Type IV collagenase;

MMP-10, also known as stromelysin-2;

MMP-11, also known as stromelysin-3;

MMP-12, also known as metalloelastase;

MMP-13, also known as collagenase-3;

MMP-14, also known as membrane-type ("MT") 1-MMP or MT1-MMP;

MMP-15, also known as MT2-MMP;

MMP-16, also known as MT3-MMP;

MMP-17, also known as MT4-MMP;

MMP-18; and

MMP-19.

Other known MMPs include MMP-26 (Matrilysin-2).

The phrase "allosteric inhibitor of MMP-13" means an inhibitor that binds to, coordinates to, or ligates a site in an MMP-13 enzyme that is at a location other than the enzyme's catalytically active site, wherein the catalytically active site is the site where the catalytic zinc cation of the MMP-13 enzyme binds, ligates, or coordinates a natural substrate(s). Thus an allosteric inhibitor of MMP-13 is any inhibitor of an MMP-13 that does not bind to, coordinate to, or ligate, either directly or indirectly via a bridging water molecule, the catalytic zinc cation of a MMP-13.

Further, an allosteric inhibitor of MMP-13, as used in the present invention, is a compound that does not ligate, coordinate to, or bind to the catalytic zinc cation of MMP-13, or a truncated form thereof, and is ≥5 times more potent in vitro versus MMP-13, or a truncated form thereof, than versus at least 2 other matrix metalloproteinase enzymes, including MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-14, MMP-17, MMP-18, MMP-19, MMP-21, and MMP-26, and tumor necrosis factor alpha convertase ("TACE"). A preferred aspect of the present invention is combinations comprising allosteric inhibitors of MMP-13 that are selective inhibitors of MMP-13 over MMP-1.

Other aspects of the present invention are allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, that are ≥10, ≥20, ≥50, ≥100, or ≥1000 times more potent versus MMP-13 than versus at least two of any other MMP enzyme or TACE.

Still other aspects of the present invention are allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, that are selective inhibitors of MMP-13 versus 2, 3, 4, 5, 6, or 7 other MMP enzymes, or versus TACE and 1, 2, 3, 4, 5, 6, or 7 other MMP enzymes.

It should be appreciated that selectivity of an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, is a multidimensional characteristic that includes the number of other MMP enzymes and TACE over which selectivity for MMP-13 inhibition is present and the degree of selectivity of inhibition of MMP-13 over another particular MMP or TACE, as measured by, for example, the IC_{50} in micromolar concentration of inhibitor for the inhibition of the other MMP enzyme or TACE divided by the IC_{50} in micromolar concentration of inhibitor for the inhibition of MMP-13.

The phrase "hydrophobic group" means a functional group in an allosteric inhibitor of an MMP-13 enzyme that lack's an affinity for water. Illustrative examples of a hydrophobic group include

C_4-C_{10} n-alkyl;

C_4-C_{10} n-alkenyl;

C_4-C_{10} n-alkynyl, wherein the C_4-C_{10} n-alkyl, C_4-C_{10} n-alkenyl, and C_4-C_{10} n-alkynyl optionally contain an O or S in place of a carbon atom,

8-membered to 10-membered fused bicyclic ring containing carbon atoms;

5-membered or 6-membered cycloalkyl;

phenyl; and

5-membered or 6-membered heteroaryl containing carbon atoms and from 1 to 3 heteroatoms independently selected from O, S, N, and N-R, wherein R is H or C_1-C_4 alkyl.

wherein the 6-membered cycloalkyl and phenyl are unsubstituted or monosubstituted in the 4-position or disubstituted in the 3-position and 4-position, wherein the substituents are selected from C_1-C_4 alkyl, O-(C_1-C_4 alkyl), S-(C_1-C_4 alkyl), and NR_aR_b, wherein R_a and R_b are each independently selected from C_1-C_4 alkyl.

The phrase "hydrogen bond acceptor" means a functional group in an allosteric inhibitor of an MMP-13 enzyme that contains an electronegative atom that

may form an electrostatic interaction with an HO-, HN<, or HS- functional group in an MMP-13 enzyme. Illustrative examples of hydrogen bond acceptor groups include OH, O-R, SH, S-R, NR^aR^b, fluoro, CN, oxo, thioxo, $=N-R^c$, NO_2, CO_2R, $C(O)NR^aR^b$, $C(S)NR^aR^b$, S(O)R, $S(O)_2R$, a 5-membered or 6-membered heteroaromatic as defined below, and a 3-membered to 6-membered heterocycloalkyl as defined below, wherein R, R^a, and R^b, are each independently selected from H, C_1-C_4 alkyl, C(O)-H, C(O)-(C_1-C_4 alkyl), and C(S)-(C_1-C_4 alkyl), and R^c is H, OH, or CN.

The term "centroid" means a center of mass.

The term "Å" means angstrom.

The term "tolerance" means the range of deviation expressed in angstroms permitted in the relative position(s) of a functional group(s).

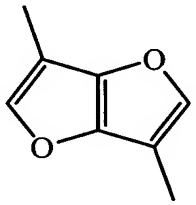
The phrase "relative position" means a position in three dimensions of a second, third, or fourth, and so on, functional group relative to a first functional group that is at a centroid position.

The phrase "Cartesian coordinate" means any of three coordinates that locate a point in space and measure its distance from any of three intersecting coordinate planes measured parallel to that one of three straight-line axes that is the intersection of the other two planes.

The phrase "monocyclic scaffold" means a phenylene or a 5-membered or 6-membered monocyclic heteroaromatic ring diradical containing carbon atoms and from 1 to 4 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the monocyclic scaffold is unsubstituted or substituted with 1 or 2 groups selected from: halo, methyl, and methoxy. Illustrative examples of a monocyclic scaffold include phenylene, isoxazoldiyl, pyrroldiyl, pyridindiyl, fluoropyridindiyl, and the like.

The phrase "bicyclic scaffold" means a fused bicyclic ring diradical, wherein a first ring is fused to a second ring, selected from: naphthalene and an 8-membered to 10-membered fused heteroaromatic bicyclic ring containing carbon atoms and optionally from 1 to 4 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein at least one ring of the fused bicyclic ring is phenylene or a 5-membered or 6-membered heteroaromatic ring containing

carbon atoms and from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the scaffold is unsubstituted or substituted with from 1 to 3 groups selected from: halo, methyl, and methoxy. Illustrative examples of bicyclic scaffolds include naphthalendiyl, indoldiyl, 2,3-dihydroindoldiyl, benzotriazoldiyl, phthalimid-diyl, 1,3-methylenedioxobenzendiyl, and the compound of formula (a)

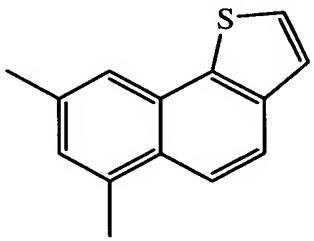


(a)

The phrase "tricyclic scaffold" means a bis-fused tricyclic ring diradical, wherein a first ring is fused to a second ring, which is fused to a third ring, selected from:

a bis-fused 14-membered aromatic tricyclic ring diradical of molecular formula $C_{14}H_8$; and

a bis-fused 10-membered to 14-membered heteroaromatic tricyclic ring diradical containing carbon atoms and from 1 to 6 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein at least one ring of the bis-fused heteroaromatic tricyclic ring diradical is a phenylene or a 5-membered or 6-membered heteroaromatic ring containing carbon atoms and from 1 to 3 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the scaffold is unsubstituted or substituted with from 1 to 5 groups selected from: halo, methyl, and methoxy. Illustrative examples of bicyclic scaffolds include anthracendiyl, dibenzofurandiyl, 1,8-naphalimid-diyl, 2,3-naphalimid-diyl, and the compound of formula (b)



(b)

The term "phenylene" means an aromatic monocyclic diradical of formula C_6H_4, or C_6H_3 in the case of a fused phenylene, which may be unsubstituted or substituted as described above.

The term "heteroaromatic" means an aromatic ring containing carbon atoms and heteroatoms as defined above.

The phrase "5-membered or 6-membered heteroaryl" means a monocyclic radical containing carbon atoms and from 1 to 4 heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_4 alkyl, which may be unsubstituted or substituted with from 1 to 3 substituents independently selected from: C_1-C_4 alkyl, oxo, thioxo, OH, O-(C_1-C_4 alkyl), SH, S-(C_1-C_4 alkyl), and NR_aR_b, wherein R_a and R_b are each independently selected from H and C_1-C_4 alkyl. Illustrative examples of 5-membered or 6-membered heteroaryl include tetrazolyl, thienyl, pyridinyl, pyrimidinyl, 3-fluoroisoxazolyl, and the like.

The phrase "linker chain" means a straight or branched alkylene diradical group of from 1 to 5 carbon atoms, or a straight or branched, 1-membered to 5-membered heteroalkylene diradical group containing carbon atoms and 1 or 2 heteroatoms selected from O, S, and N-R, wherein R is H or C_1-C_6 alkyl, wherein the alkylene and heteroalkylene groups are unsubstituted or substituted with from 1 to 3 substituents selected from oxo ("=O"), thioxo ("=S"), =N-CN, fluoro, methoxy, and CN. Illustrative examples of linker chains include CH_2, $CH(CH_3)$, C=O, $CH_2C(O)NH$, $O(CH_2)_2$, $(CH_2)_3$, and the like.

The phrase "alkylene of from 1 to 5 carbon atoms" means a carbon chain diradical which is straight or branched, unsubstituted or substituted with from 1 to 3 substituents selected from: oxo ("=O"), thioxo ("=S"), =N-CN, fluoro, methoxy, and CN. Illustrative examples of alkylenes of from 1 to 5 carbon atoms include CH_2, $CH(CH_3)$, C=O, $(CH_2)_3$, and the like.

The phrase "1-membered to 5-membered heteroalkylene" means a chain diradical containing from 0 to 4 carbon atoms and 1 or 2 heteroatoms selected from O, S, and N-R, wherein R is H or C_1-C_6 alkyl, which is straight or branched, unsubstituted or substituted with from 1 to 3 substituents selected from: oxo ("=O"), thioxo ("=S"), =N-CN, fluoro, methoxy, and CN. Illustrative examples of

1-membered to 5-membered heteroalkylenes include $CH_2C(O)NH$, $O(CH_2)_2$, and the like.

The phrase "5-membered or 6-membered cycloalkyl" means a cyclopentyl or cyclohexyl group, which is unsubstituted or substituted with 1 or 2 substituents independently selected from: C_1-C_4 alkyl, oxo, thioxo, =N-CN, OH, O-(C_1-C_4 alkyl), SH, S-(C_1-C_4 alkyl), and NR_aR_b, wherein R_a and R_b are each independently selected from H and C_1-C_4 alkyl.

The phrase "5-membered or 6-membered heterocycloalkyl" means a cyclopentyl or cyclohexyl group, wherein from 1 to 3 carbon atoms are replaced with heteroatoms selected from O, S, N, and N-R, wherein R is H or C_1-C_4alkyl, which is unsubstituted or substituted with 1 or 2 substituents independently selected from: C_1-C_4 alkyl, oxo, thioxo, OH, O-(C_1-C_4 alkyl), SH, S-(C_1-C_4 alkyl), and NR_aR_b, wherein R_a and R_b are each independently selected from H and C_1-C_4 alkyl.

The term "Thr245" means threonine 245 of an MMP-13 enzyme.

The term "Thr247" means threonine 247 of an MMP-13 enzyme.

The term "Met253" means methionine 253 of an MMP-13 enzyme.

The term "His251" means histidine 251 of an MMP-13 enzyme.

The term "C_4-C_{10} n-alkyl" means a normal alkyl group of from 4 to 10 carbon atoms. Illustrative examples of C_4-C_{10} n-alkyl include n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, and n-decyl. The group C_4-C_{10} n-alkyl may optionally contain an O or S in place of a carbon atom. Illustrative examples of C_4-C_{10} n-alkyl optionally containing an O or S in place of a carbon atom include n-butoxy, n-propyloxymethyl, and 10-hydroxy-n-decyl.

The term "C_4-C_{10} n-alkenyl" means a normal alkenyl group of from 4 to 10 carbon atoms. Illustrative examples of C_4-C_{10} n-alkenyl include n-2-buten-1-yl, n-2-penten-3-yl, n-5-hexen-1-yl, n-1-hepten-2-yl, n-1-octen-1-yl, n-8-nonen-2-yl, and n-4-decen-4-yl. The group C_4-C_{10} n-alkenyl may optionally contain an O or S in place of a carbon atom. Illustrative examples of C_4-C_{10} n-alkenyl optionally containing an O or S in place of a carbon atom include n-2-butenoxy, n-2-propenyloxymethyl, and 10-hydroxy-n-1-decenyl.

The term "C_4-C_{10} n-alkynyl" means a normal alkynyl group of from 4 to 10 carbon atoms. Examples of C_4-C_{10} n-alkynyl include n-2-butyn-1-yl, n-2-pentyn-4-yl, n-5-hexyn-1-yl, n-1-heptyn-3-yl, n-1-octyn-1-yl, n-8-nonyn-2-yl, and n-4-decyn-1-yl. The group C_4-C_{10} n-alkynyl may optionally contain an O or S in place of a carbon atom. Illustrative examples of C_4-C_{10} n-alkynyl optionally containing an O or S in place of a carbon atom include n-2-butynoxy, n-2-propynyloxymethyl, and 10-hydroxy-n-1-decynyl.

The term "C_1-C_4 alkyl" means a hydrocarbon radical of from 1 to 4 carbon atoms, which is straight or branched, unsubstituted or substituted with from 1 to 3 groups independently selected from fluoro and CN.

The term "O-(C_1-C_4 alkyl) means a C_1-C_4 alkyl group as defined above bonded to an oxygen radical.

The term "S-(C_1-C_4 alkyl) means a C_1-C_4 alkyl group as defined above bonded to an sulfur radical.

The term "halo" includes fluoro, chloro, bromo, and iodo.

The phrase "linker chain atom" means an atom of the linker chain as defined above.

The phrase "separated by two atoms" and "two atoms distance" are synonymous and refer to the separation between two groups, and mean that one of the two groups being separated is bonded to a first atom of the two atoms, which first atom is in turn bonded to a second atom of the two atoms, which second atom is in turn bonded to the second of the two groups being separated.

It should be appreciated that an atom in the scaffold, or the atom in a linker chain that is directly bonded to a scaffold, may comprise a hydrogen bond acceptor group as defined above. Illustrative examples of an atom in a scaffold comprising a hydrogen bond acceptor group includes scaffolds containing a carbon atom substituted with oxo ("=O") or fluoro. Illustrative examples of an atom in a linker chain that is directly bonded to a scaffold comprising a hydrogen bond acceptor group includes linker chains wherein the atom that is directly bonded to the scaffold is an O or S, or wherein the atom that is directly bonded to the scaffold comprises a carbonyl diradical (">C=O") or a diradical which is CHF or CF_2.

It should be appreciated that the first ring of the bicyclic or tricyclic scaffolds is, unless otherwise specified herein, the ring bonded to the hydrophobic group or, where there are two hydrophobic groups, the first hydrophobic group.

It should be appreciated that the junction of a scaffold and a substituent on the scaffold means the atom of the scaffold bearing the substituent.

The phrase "fused bicyclic ring" means a first ring and a second ring, wherein the first ring and second ring share two, and only two, atoms, which two atoms may be referred to herein as first and second atom junctions. It should be further appreciated that the atoms of the first ring and second ring that are each bonded to the first atom junction may be referred to herein as the first nonjunction atoms, and the atoms of the first ring and second ring that are each bonded to the second atom junction may be referred to herein as the second nonjunction atoms.

It should be appreciated that a bis-fused tricyclic ring means three rings, a first ring, a second ring, and a third ring, wherein the first ring and the second ring share two, and only two atoms, which two atoms may be referred to herein as first and second atom junctions, and the second ring and the third ring share two, and only two, atoms, which two atoms may be referred to herein as third and fourth atom junctions. It should be further appreciated that the atoms of the first ring and second ring that are each bonded to the first atom junction may be referred to herein as the first nonjunction atoms of the first and second rings, respectively, and the atoms of the first ring and second ring that are each bonded to the second atom junction may be referred to herein as the second nonjunction atoms of the first and second rings, respectively. It should be further appreciated that the atoms of the second ring and third ring that are each bonded to the third atom junction may be referred to herein as the third nonjunction atoms of the first and second rings, respectively, and the atoms of the second ring and third ring that are each bonded to the fourth atom junction may be referred to herein as the fourth nonjunction atoms of the first and second rings, respectively.

Unless substituents are otherwise defined, a compound of the invention may be optionally substituted from 1 to 3 times at any of from 1 to 3 carbon atoms, respectively, wherein each carbon atom is capable of substitution by replacement of a hydrogen atom with a group independently selected from:

C_1-C_4 alkyl;

C_2-C_4 alkenyl;

C_2-C_4 alkynyl;

CF_3;

halo;

OH;

O-(C_1-C_4 alkyl);

OCH_2F;

$OCHF_2$;

OCF_3;

OC(O)-(C_1-C_4 alkyl);

OC(O)O-(C_1-C_4 alkyl);

OC(O)NH-(C_1-C_4 alkyl);

OC(O)N(C_1-C_4 alkyl)$_2$;

OC(S)NH-(C_1-C_4 alkyl);

OC(S)N(C_1-C_4 alkyl)$_2$;

SH;

S-(C_1-C_4 alkyl);

S(O)-(C_1-C_4 alkyl);

$S(O)_2$-(C_1-C_4 alkyl);

SC(O)-(C_1-C_4 alkyl);

SC(O)O-(C_1-C_4 alkyl);

NH_2;

N(H)-(C_1-C_4 alkyl);

N(C_1-C_4 alkyl)$_2$;

N(H)C(O)-(C_1-C_4 alkyl);

$N(CH_3)C(O)$-(C_1-C_4 alkyl);

$N(H)C(O)$-CF_3;

$N(CH_3)C(O)$-CF_3;

N(H)C(S)-(C_1-C_4 alkyl);

$N(CH_3)C(S)$-(C_1-C_4 alkyl);

$N(H)S(O)_2$-(C_1-C_4 alkyl);

$N(H)C(O)NH_2$;

$N(H)C(O)NH$-(C_1-C_4 alkyl);

$N(CH_3)C(O)NH$-(C_1-C_4 alkyl);

$N(H)C(O)N(C_1$-C_4 alkyl$)_2$;

$N(CH_3)C(O)N(C_1$-C_4 alkyl$)_2$;

$N(H)S(O)_2NH_2$;

$N(H)S(O)_2NH$-(C_1-C_4 alkyl);

$N(CH_3)S(O)_2NH$-(C_1-C_4 alkyl);

$N(H)S(O)_2N(C_1$-C_4 alkyl$)_2$;

$N(CH_3)S(O)_2N(C_1$-C_4 alkyl$)_2$;

$N(H)C(O)O$-(C_1-C_4 alkyl);

$N(CH_3)C(O)O$-(C_1-C_4 alkyl);

$N(H)S(O)_2O$-(C_1-C_4 alkyl);

$N(CH_3)S(O)_2O$-(C_1-C_4 alkyl);

$N(CH_3)C(S)NH$-(C_1-C_4 alkyl);

$N(CH_3)C(S)N(C_1$-C_4 alkyl$)_2$;

$N(CH_3)C(S)O$-(C_1-C_4 alkyl);

$N(H)C(S)NH_2$;

NO_2;

CO_2H;

CO_2-(C_1-C_4 alkyl);

$C(O)N(H)OH$;

$C(O)N(CH_3)OH$;

$C(O)N(CH_3)OH$;

$C(O)N(CH_3)O$-(C_1-C_4 alkyl);

$C(O)N(H)$-(C_1-C_4 alkyl);

$C(O)N(C_1$-C_4 alkyl$)_2$;

$C(S)N(H)$-(C_1-C_4 alkyl);

$C(S)N(C_1$-C_4 alkyl$)_2$;

$C(NH)N(H)$-(C_1-C_4 alkyl);

$C(NH)N(C_1$-C_4 alkyl$)_2$;

$C(NCH_3)N(H)$-(C_1-C_4 alkyl);

$C(NCH_3)N(C_1\text{-}C_4\ alkyl)_2$;

$C(O)\text{-}(C_1\text{-}C_4\ alkyl)$;

$C(NH)\text{-}(C_1\text{-}C_4\ alkyl)$;

$C(NCH_3)\text{-}(C_1\text{-}C_4\ alkyl)$;

$C(NOH)\text{-}(C_1\text{-}C_4\ alkyl)$;

$C(NOCH_3)\text{-}(C_1\text{-}C_4\ alkyl)$;

CN;

CHO;

CH_2OH;

$CH_2O\text{-}(C_1\text{-}C_4\ alkyl)$;

CH_2NH_2;

$CH_2N(H)\text{-}(C_1\text{-}C_4\ alkyl)$; and

$CH_2N(C_1\text{-}C_4\ alkyl)_2$; wherein

"C_1-C_4 alkyl" means a straight or branched, unsubstituted alkyl chain of from 1 to 4 carbon atoms;

"C_2-C_4 alkenyl" means a straight or branched, unsubstituted alkenyl chain of from 2 to 4 carbon atoms; and

"C_2-C_4 alkynyl" means a straight or branched, unsubstituted alkynyl chain of from 2 to 4 carbon atoms.

The term "IC_{50}" means the concentration of a compound, usually expressed as micromolar or nanomolar, required to inhibit an enzyme's catalytic activity by 50%.

The term "ED_{40}" means the concentration of a compound, usually expressed as micromolar or nanomolar, required to treat a disease in 40% of a patient group.

The term "ED_{30}" means the concentration of a compound, usually expressed as micromolar or nanomolar, required to treat a disease in 30% of a patient group.

The phrase "pharmaceutical composition" means a composition suitable for administration in medical or veterinary use.

The term "admixed" and the phrase "in admixture" are synonymous and mean in a state of being in a homogeneous or heterogeneous mixture. Preferred is a homogeneous mixture.

As used herein, the phrase "cartilage damage" means a disorder of hyaline cartilage and subchondral bone characterized by hypertrophy of tissues in and around the involved joints, which may or may not be accompanied by deterioration of hyaline cartilage surface.

The term "treating", which also is related to derivatives thereof such as "treat" or "treated", means administration of an invention combination as defined above that inhibits the progress, prevents further progress, or reverses progression, in part or in whole, of any one or more symptoms of any one of the diseases and disorders listed above.

The term "comprising," which is synonymous with the terms "including," "containing," or "characterized by," is inclusive or open-ended, and does not exclude additional, unrecited elements or method steps from the scope of the invention that is described following the term.

The phrase "consisting of " is closed-ended, and excludes any element, step, or ingredient not specified in the description of the invention that follows the phrase.

The phrase "consisting essentially of" limits the scope of the invention that follows to the specified elements, steps, or ingredients, and those further elements, steps, or ingredients that do not materially affect the basic and novel characteristics of the invention.

The invention combination also includes isotopically-labelled compounds, which are identical to those recited above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds of the present invention and pharmaceutically acceptable salts of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution

assays. Tritiated, *i.e.*, ^{3}H and carbon-14, *i.e.*, ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, *i.e.*, ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of those described above in this invention can generally be prepared by carrying out the procedures incorporated by reference above or disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

One of ordinary skill in the art will appreciate that the combinations of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the combinations of the invention in the treatment of a specific disease that the combinations of the invention may be combined with various existing therapeutic agents used for that disease.

For the treatment of rheumatoid arthritis, the combinations of the invention may be combined with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel®), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The combinations of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors that are not celecoxib and valdecoxib, such as etoricoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

This invention also relates to a method of or a pharmaceutical composition for treating inflammatory processes and diseases comprising administering a

combination of this invention to a mammal, including a human, cat, livestock or dog, wherein said inflammatory processes and diseases are defined as above and said inhibitory combination is used in combination with one or more other therapeutically active agents under the following conditions:

A.) where a joint has become seriously inflamed as well as infected at the same time by bacteria, fungi, protozoa and/or virus, said inhibitory combination is administered in combination with one or more antibiotic, antifungal, antiprotozoal and/or antiviral therapeutic agents;

B.) where a multi-fold treatment of pain and inflammation is desired, said inhibitory combination is administered in combination with inhibitors of other mediators of inflammation, comprising one or more members independently selected from the group consisting essentially of:

(1) NSAIDs;

(2) H_1 -receptor antagonists;

(3) kinin-B_1 - and B_2 -receptor antagonists;

(4) prostaglandin inhibitors selected from the group consisting of PGD-, PGF- PGI_2 - and PGE-receptor antagonists;

(5) thromboxane A_2 (TXA_2-) inhibitors;

(6) 5-, 12- and 15-lipoxygenase inhibitors;

(7) leukotriene LTC_4 -, LTD_4/LTE_4 - and LTB_4 -inhibitors;

(8) PAF-receptor antagonists;

(9) gold in the form of an aurothio group together with one or more hydrophilic groups;

(10) immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine and methotrexate;

(11) anti-inflammatory glucocorticoids;

(12) penicillamine;

(13) hydroxychloroquine;

(14) anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone and benzbromarone;

C. where older mammals are being treated for disease conditions, syndromes and symptoms found in geriatric mammals, said inhibitory combination is administered in combination with one or more members independently selected from the group consisting essentially of:

(1) cognitive therapeutics to counteract memory loss and impairment;

(2) anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure and myocardial infarction, selected from the group consisting of:

a. diuretics;

b. vasodilators;

c. β-adrenergic receptor antagonists;

d. angiotensin-II converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;

e. angiotensin II receptor antagonists;

f. renin inhibitors;

g. calcium channel blockers;

h. sympatholytic agents;

i. α_2-adrenergic agonists;

j. α-adrenergic receptor antagonists; and

k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

(3) antineoplastic agents selected from:

a. antimitotic drugs selected from:

i. vinca alkaloids selected from:

[1] vinblastine and

[2] vincristine;

(4) growth hormone secretagogues;

(5) strong analgesics;

(6) local and systemic anesthetics; and

(7) H_2 -receptor antagonists, proton pump inhibitors and other gastroprotective agents.

The active ingredient of the present invention may be administered in combination with inhibitors of other mediators of inflammation, comprising one or more members selected from the group consisting essentially of the classes of such inhibitors and examples thereof which include, matrix metalloproteinase inhibitors, aggrecanase inhibitors, TACE inhibitors, leucotriene receptor antagonists, IL-1 processing and release inhibitors, ILra, H_1 -receptor antagonists; kinin-B_1 - and B_2 -receptor antagonists; prostaglandin inhibitors such as PGD-, PGF- PGI_2 - and PGE-receptor antagonists; thromboxane A_2 (TXA2-) inhibitors; 5- and 12-lipoxygenase inhibitors; leukotriene LTC_4 -, LTD_4/LTE_4 - and LTB_4 - inhibitors; PAF-receptor antagonists; gold in the form of an aurothio group together with various hydrophilic groups; immunosuppressive agents, *e.g.*, cyclosporine, azathioprine and methotrexate; anti-inflammatory glucocorticoids; penicillamine; hydroxychloroquine; anti-gout agents, *e.g.*, colchicine, xanthine oxidase inhibitors, *e.g.*, allopurinol and uricosuric agents, *e.g.*, probenecid, sulfinpyrazone and benzbromarone.

The combinations of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine and antimetabolites such as methotrexate.

The combinations of the present invention may also be used in combination with anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, including hypertension, myocardial ischemia including angina, congestive heart failure and myocardial infarction, selected from vasodilators such as hydralazine, β-adrenergic receptor antagonists such as propranolol, calcium channel blockers such as nifedipine, α_2-adrenergic agonists such as clonidine, α-adrenergic receptor antagonists such as prazosin and HMG-CoA-reductase inhibitors (anti-hypercholesterolemics) such as lovastatin or atorvastatin.

The combination of the present invention may also be administered in combination with one or more antibiotic, antifungal, antiprotozoal, antiviral or similar therapeutic agents.

The combinations of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as L-dopa, requip, mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal nitric oxide synthase) and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors except celecoxib and valdecoxib, propentofylline or metryfonate.

The combinations of the present invention may also be used in combination with osteoporosis agents such as roloxifene, lasofoxifene, droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

The present invention also relates to the formulation of the combination of the present invention alone or with one or more other therapeutic agents which are to form the intended combination, including wherein said different drugs have varying half-lives, by creating controlled-release forms of said drugs with different release times which achieves relatively uniform dosing; or, in the case of non-human patients, a medicated feed dosage form in which said drugs used in the combination are present together in admixture in the feed composition. There is further provided in accordance with the present invention co-administration in which the combination of drugs is achieved by the simultaneous administration of said drugs to be given in combination; including co-administration by means of different dosage forms and routes of administration; the use of combinations in accordance with different but regular and continuous dosing schedules whereby desired plasma levels of said drugs involved are maintained in the patient being treated, even though the individual drugs making up said combination are not being administered to said patient simultaneously.

The term "drugs", which is synonymous with the phrases "active components", "active compounds", and "active ingredients", includes a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, an NSAID, or a pharmaceutically

acceptable salt thereof, and may further include one or two of the other therapeutic agents described above.

The invention method is useful in human and veterinary medicines for treating mammals suffering from one or more of the above-listed diseases and disorders.

The term "mammal" includes humans, companion animals such as cats and dogs, primates such as monkeys and chimpanzees, and livestock animals such as horses, cows, pigs, and sheep.

The phrase "livestock animals" as used herein refers to domesticated quadrupeds, which includes those being raised for meat and various byproducts, *e.g.,* a bovine animal including cattle and other members of the genus *Bos*, a porcine animal including domestic swine and other members of the genus *Sus*, an ovine animal including sheep and other members of the genus *Ovis*, domestic goats and other members of the genus *Capra*; domesticated quadrupeds being raised for specialized tasks such as use as a beast of burden, *e.g.,* an equine animal including domestic horses and other members of the family Equidae, genus *Equus*, or for searching and sentinel duty, *e.g.,* a canine animal including domestic dogs and other members of the genus *Canis*; and domesticated quadrupeds being raised primarily for recreational purposes, *e.g.,* members of *Equus* and *Canis*, as well as a feline animal including domestic cats and other members of the family Felidae, genus *Felis*.

All that is required to practice the method of this invention is to administer a combination of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, in an amount that is therapeutically effective for preventing, inhibiting, or reversing the condition being treated. The invention combination can be administered directly or in a pharmaceutical composition as described below.

A therapeutically effective amount, or, simply, effective amount, of an invention combination will generally be from about 1 to about 300 mg/kg of subject body weight of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and from about 1 to

about 300 mg/kg of subject body weight of an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof. Typical doses will be from about 10 to about 5000 mg/day for an adult subject of normal weight for each component of the combination. In a clinical setting, regulatory agencies such as, for example, the Food and Drug Administration ("FDA") in the U.S. may require a particular therapeutically effective amount.

In determining what constitutes an effective amount or a therapeutically effective amount of an invention combination for treating, preventing, or reversing one or more symptoms of any one of the diseases and disorders described above that are being treated according to the invention methods, a number of factors will generally be considered by the medical practitioner or veterinarian in view of the experience of the medical practitioner or veterinarian, including the Food and Drug Administration guidelines, or guidelines from an equivalent agency, published clinical studies, the subject's (e.g., mammal's) age, sex, weight and general condition, as well as the type and extent of the disease, disorder or condition being treated, and the use of other medications, if any, by the subject. As such, the administered dose may fall within the ranges or concentrations recited above, or may vary outside them, ie, either below or above those ranges, depending upon the requirements of the individual subject, the severity of the condition being treated, and the particular therapeutic formulation being employed. Determination of a proper dose for a particular situation is within the skill of the medical or veterinary arts. Generally, treatment may be initiated using smaller dosages of the invention combination that are less than optimum for a particular subject. Thereafter, the dosage can be increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Pharmaceutical compositions, described briefly here and more fully below, of an invention combination may be produced by formulating the invention combination in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers

containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Alternatively, the active components of the invention combination may be formulated separately.

Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch; cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations.

The compositions to be employed in the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents commonly employed to treat any of the above-listed diseases and disorders.

The percentage of the active ingredients of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, combination in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a total concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredients are present, for example, up to about 95%.

Preferred routes of administration of an invention combination are oral or parenteral. However, another route of administration may be preferred depending upon the condition being treated. For exampled, topical administration or administration by injection may be preferred for treating conditions localized to the skin or a joint. Administration by transdermal patch may be preferred where, for example, it is desirable to effect sustained dosing.

It should be appreciated that the different routes of administration may require different dosages. For example, a useful intravenous ("IV") dose is between 5 and 50 mg, and a useful oral dosage is between 20 and 800 mg, both for each of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof. The dosage is within the dosing range used in treatment of the above-listed diseases, or as would be determined by the needs of the patient as described by the physician.

The invention combination may be administered in any form. Preferably, administration is in unit dosage form. A unit dosage form of the invention combination to be used in this invention may also comprise other compounds useful in the therapy of diseases described above. A further description of pharmaceutical formulations useful for administering the invention combinations is provided below.

The active components of the invention combination, including a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and other compounds as described above, if any, may be formulated together or separately and may be administered together or separately. The particular formulation and administration regimens used may be tailored to the particular patient and condition being treated by a practitioner of ordinary skill in the medical or pharmaceutical arts.

The advantages of using an invention combination comprising a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, in a method of the instant invention include the nontoxic nature of the compounds which comprise the combination at and substantially above therapeutically effective doses, their ease of preparation, the fact that the compounds are well-tolerated, and the ease of topical, IV, or oral administration of the drugs.

Another important advantage is that the present invention combinations more effectively target a particular disease that is responsive to inhibition of

MMP-13 with fewer undesirable side effects than similar combinations that contain MMP-13 inhibitors that are not allosteric inhibitors of MMP-13. This is so because the instant allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, do not directly, or indirectly via a bridging water molecule, ligate, coordinate to, or bind to the catalytic zinc cation of MMP-13, but instead bind at a different location from where natural substrate binds to MMP-13. The binding requirements of an allosteric MMP-13 binding site are unique to MMP-13, and account for the specificity of the instant allosteric inhibitors of MMP-13 for inhibiting MMP-13 over any other MMP enzyme. This binding mode has not been reported in the art. Indeed, prior art inhibitors of MMP-13 bind to the catalytic zinc cations of other MMP enzymes as well as to the catalytic zinc cation of MMP-13 and, and are consequently significantly less selective inhibitors of MMP-13 enzyme.

The instant allosteric inhibitors of MMP-13 are thus therapeutically superior to other inhibitors of MMP-13, or even tumor necrosis factor-alpha converting enzyme ("TACE"), because of fewer undesirable side effects from inhibition of the other MMP enzymes or TACE. For example, virtually all prior art MMP inhibitors tested clinically to date have exhibited an undesirable side effect known as muscoloskeletal syndrome ("MSS"). MSS is associated with administering an inhibitor of multiple MMP enzymes or an inhibitor of a particular MMP enzyme such as MMP-1. MSS will be significantly reduced in type and severity by administering the invention combination instead of any combination of a prior art MMP-13 inhibitor with celecoxib or valdecoxib, or a pharmaceutically acceptable salt thereof. The invention combinations are superior to similar combinations that include a COX-2 selective inhibitor with an MMP inhibitor that interacts with the catalytic zinc cation of the MMP-13 enzyme as discussed above, even if that inhibitor shows some selectivity for the MMP-13.

This advantage of the instant combinations will also significantly increase the likelihood that agencies which regulate new drug approvals, such as the United States Food and Drug Administration, will approve the instant combination versus a competing similar combination as discussed above even in the unlikely event that the two combinations behaved similarly in clinical trials.

These regulatory agencies are increasingly aware that clinical trials, which test drug in limited population groups, do not always uncover safety problems with a drug, and thus all other things being equal, the agencies will favor the drug with the lowest odds of producing undesirable side effects.

Another important advantage is that the independent anti-inflammatory and pain reducing properties described above for a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib and the disease modifying properties of allosteric inhibitors of MMP-13 provide patients suffering from cartilage damage, arthritis, preferably osteoarthritis, inflammation and/or pain with both relief of symptoms and prevention or inhibition of the underlying disease pathology such as cartilage degradation.

A further advantage of the invention combination is administration of the invention combination to treat a disease or disorder in a mammal may allow lower doses of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and/or an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, of the combination to be used than would be used if a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and the allosteric inhibitor of MMP-13 were each administered alone. Another expected advantage is that two therapeutically beneficial effects, e.g., inhibiting cartilage damage and alleviating pain, are obtainable with the invention combination whereas just one of those effects is possible with a single active component of the combination.

Some of the compounds utilized in an invention combination are capable of further forming pharmaceutically acceptable salts, including, but not limited to, acid addition and/or base salts. The acid addition salts are formed from basic compounds, whereas the base addition salts are formed from acidic compounds. All of these forms are within the scope of the compounds useful in the invention combination.

Pharmaceutically acceptable acid addition salts of the basic compounds useful in the invention combination include nontoxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well nontoxic salts derived from

organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, malate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *J. of Pharma. Sci.*, 1977;66:1).

An acid addition salt of a basic compound useful in the invention combination is prepared by contacting the free base form of the compound with a sufficient amount of a desired acid to produce a nontoxic salt in the conventional manner. The free base form of the compound may be regenerated by contacting the acid addition salt so formed with a base, and isolating the free base form of the compound in the conventional manner. The free base forms of compounds prepared according to a process of the present invention differ from their respective acid addition salt forms somewhat in certain physical properties such as solubility, crystal structure, hygroscopicity, and the like, but otherwise free base forms of the compounds and their respective acid addition salt forms are equivalent for purposes of the present invention.

À pharmaceutically acceptable base addition salt of an acidic compound useful in the invention combination may be prepared by contacting the free acid form of the compound with a nontoxic metal cation such as an alkali or alkaline earth metal cation, or an amine, especially an organic amine. Examples of suitable metal cations include sodium cation (Na^+), potassium cation (K^+), magnesium cation (Mg^{2+}), calcium cation (Ca^{2+}), and the like. Examples of suitable amines are N,N′-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine,

dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge, supra., 1977).

A base addition salt of an acidic compound useful in the invention combination may be prepared by contacting the free acid form of the compound with a sufficient amount of a desired base to produce the salt in the conventional manner. The free acid form of the compound may be regenerated by contacting the salt form so formed with an acid, and isolating the free acid of the compound in the conventional manner. The free acid forms of the compounds useful in the invention combination differ from their respective salt forms somewhat in certain physical properties such as solubility, crystal structure, hygroscopicity, and the like, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds useful in the invention combination can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are encompassed within the scope of the present invention.

Certain of the compounds useful in the invention combination possess one or more chiral centers, and each center may exist in the R or S configuration. An invention combination may utilize any diastereomeric, enantiomeric, or epimeric form of a compound useful in the invention combination, as well as mixtures thereof.

Additionally, certain compounds useful in the invention combination may exist as geometric isomers such as the entgegen (E) and zusammen (Z) isomers of 1,2-disubstituted alkenyl groups or cis and trans isomers of disubstituted cyclic groups. An invention combination may utilize any cis, trans, syn, anti, entgegen (E), or zusammen (Z) isomer of a compound useful in the invention combination, as well as mixtures thereof.

Certain compounds useful in the invention combination can exist as two or more tautomeric forms. Tautomeric forms of the compounds may interchange, for example, via enolization/de-enolization, 1,2-hydride, 1,3-hydride, or 1,4-hydride shifts, and the like. An invention combination may utilize any tautomeric form of a compound useful in the invention combination, as well as mixtures thereof.

The syntheses of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib are well-known in the art, and have even been carried out to produce commercial-scale quantities of compound in the case of etoricoxib, for example. The synthesis of allosteric inhibitors of MMP-13 are taught in the patent applications incorporated above by reference.

Intermediates for the synthesis of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, useful in the invention combination may be prepared by one of ordinary skill in the art of organic chemistry by adapting various synthetic procedures incorporated by reference above or that are well-known in the art of organic chemistry. These synthetic procedures may be found in the literature in, for example, *Reagents for Organic Synthesis*, by Fieser and Fieser, John Wiley & Sons, Inc, New York, 2000; *Comprehensive Organic Transformations*, by Richard C. Larock, VCH Publishers, Inc, New York, 1989; the series *Compendium of Organic Synthetic Methods*,1989,by Wiley-Interscience; the text *Advanced Organic Chemistry*, 4th edition, by Jerry March, Wiley-Interscience, New York,1992; or the *Handbook of Heterocyclic Chemistry* by Alan R. Katritzky, Pergamon Press Ltd, London, 1985, to name a few. Alternatively, a skilled artisan may find methods useful for preparing the intermediates in the chemical literature by searching widely available databases such as, for example, those available from the *Chemical Abstracts Service*, Columbus, Ohio, or *MDL Information Systems GmbH* (formerly *Beilstein Information Systems GmbH*), Frankfurt, Germany.

Preparations of the compounds useful in an invention combination may use starting materials, reagents, solvents, and catalysts that may be purchased from commercial sources or they may be readily prepared by adapting procedures in the references or resources cited above. Commercial sources of starting materials, reagents, solvents, and catalysts useful in preparing invention compounds include, for example, *The Aldrich Chemical Company*, and other subsidiaries of Sigma-Aldrich Corporation, St. Louis, Missouri, *BACHEM*, BACHEM A.G., Switzerland, or *Lancaster Synthesis Ltd*, United Kingdom.

Syntheses of some compounds useful in the invention combination may utilize starting materials, intermediates, or reaction products that contain a reactive functional group. During chemical reactions, a reactive functional group may be protected from reacting by a protecting group that renders the reactive functional group substantially inert to the reaction conditions employed. A protecting group is introduced onto a starting material prior to carrying out the reaction step for which a protecting group is needed. Once the protecting group is no longer needed, the protecting group can be removed. It is well within the ordinary skill in the art to introduce protecting groups during a synthesis of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, or an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and then later remove them. Procedures for introducing and removing protecting groups are known and referenced such as, for example, in *Protective Groups in Organic Synthesis*, 2nd ed., Greene T.W. and Wuts P.G., John Wiley & Sons, New York: New York, 1991, which is hereby incorporated by reference.

Thus, for example, protecting groups such as the following may be utilized to protect amino, hydroxyl, and other groups: carboxylic acyl groups such as, for example, formyl, acetyl, and trifluoroacetyl; alkoxycarbonyl groups such as, for example, ethoxycarbonyl, *tert*-butoxycarbonyl (BOC), β,β,β-trichloroethoxycarbonyl (TCEC), and β-iodoethoxycarbonyl; aralkyloxycarbonyl groups such as, for example, benzyloxycarbonyl (CBZ), *para*-methoxybenzyloxycarbonyl, and 9-fluorenylmethyloxycarbonyl (FMOC); trialkylsilyl groups such as, for example, trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBDMS); and other groups such as, for example, triphenylmethyl (trityl), tetrahydropyranyl, vinyloxycarbonyl, *ortho*-nitrophenylsulfenyl, diphenylphosphinyl, *para*-toluenesulfonyl (Ts), mesyl, trifluoromethanesulfonyl, and benzyl. Examples of procedures for removal of protecting groups include hydrogenolysis of CBZ groups using, for example, hydrogen gas at 50 psi in the presence of a hydrogenation catalyst such as 10% palladium on carbon, acidolysis of BOC groups using, for example, hydrogen chloride in dichloromethane, trifluoroacetic acid (TFA) in dichloromethane, and

the like, reaction of silyl groups with fluoride ions, and reductive cleavage of TCEC groups with zinc metal.

For illustration purposes, examples of allosteric inhibitors of MMP-13 are described below. The allosteric inhibitors of MMP-13 have been evaluated in standard assays for their ability to inhibit the catalytic activity of various MMP enzymes. The assays used to evaluate the MMP biological activity of the invention compounds are well-known and routinely used by those skilled in the study of MMP inhibitors and their use to treat clinical conditions. For example, allosteric inhibitors of MMP-13 may be readily identified by assaying a test compound for inhibition of MMP-13 according to Biological Methods 1 or 2, and further assaying the test compound for allosteric inhibition of MMP-13 according to Biological Methods 3 or 4, as described below.

Examples of allosteric inhibitors of MMP-13 are provided below. The compounds have been shown to be potent and selective inhibitors of MMP-13 catalytic domain versus full-length MMP-1 and MMP-3 catalytic domain. Potencies with MMP-13 catalytic domain for the allosteric inhibitors of MMP-13 typically range from about 0.001 μM to about 1 μM. Some compounds were further screened with full-length MMP-2, full-length MMP-7, full-length MMP-9, and MMP-14 catalytic domain, and were found to be selective inhibitors of MMP-13 versus these other MMP enzymes also. Selectivity of the allosteric inhibitors of MMP-13 for MMP-13 catalytic domain versus another MMP enzyme (full-length or catalytic domain), as determined by dividing the IC_{50} for the inhibitor with a comparator MMP enzyme by the IC_{50} of the inhibitor with MMP-13 catalytic domain, typically ranged from 5 to 50,000 fold.

EXAMPLES OF ALLOSTERIC INHIBITORS OF MMP-13

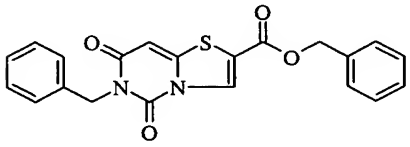
1. Examples of thiazolopyrimidinedione allosteric inhibitors of MMP-13:

The syntheses of thiazolopyrimidinediones useful as allosteric inhibitors of MMP-13 are described in our co-pending U.S. nonprovisional application number 10/071,032, the corresponding PCT International application number

PCT/IB02/00313, and the priority application U.S. provisional application number 60/268,780, filed on February 14, 2001.

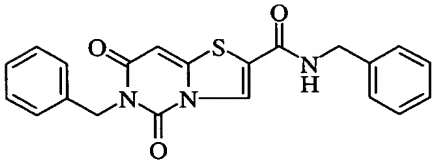
EXAMPLE 1

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester



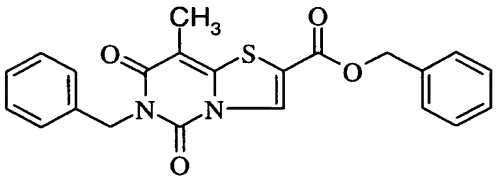
EXAMPLE 2

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide



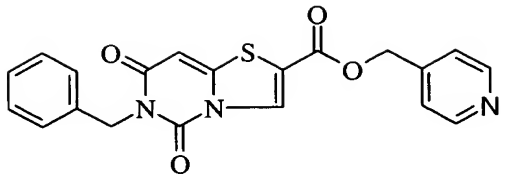
EXAMPLE 3

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester



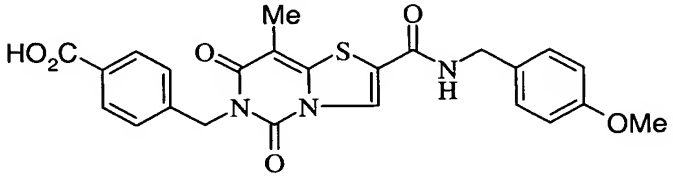
EXAMPLE 4

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid pyridin-4-ylmethyl ester hydrochloride



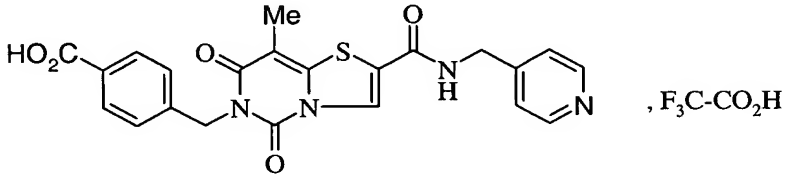
EXAMPLE 5

4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-*c*] pyrimidin-6-ylmethyl]-benzoic acid



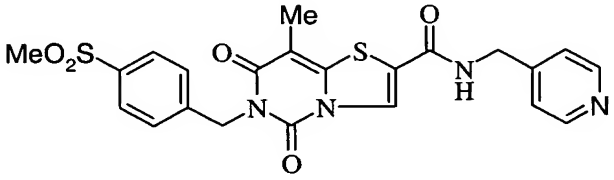
EXAMPLE 6

4-{8-Methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid trifluoro-acetate



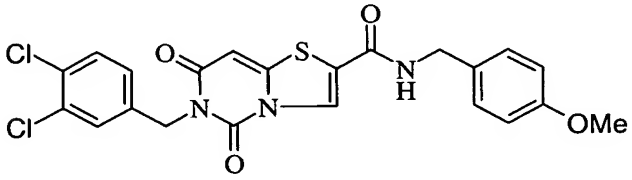
EXAMPLE 7

6-(4-Methanesulfonyl-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo [3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride



EXAMPLE 8

6-(3,4-Dichloro-benzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide



Additional Examples of thiazolopyrimidinediones are named below.

5

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-benzylamide
6-Benzoyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide
6-(3,4-Dichlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide
6-(4-Chlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide
6-(4-Chlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichlorobenzylamide
6-(4-Pyridylmethyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide hydrochloride
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxybenzylamide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichlorobenzylamide
6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid pyridin-4-ylmethyl ester hydrochloride
6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-

2-carboxylic acid (pyridin-4-ylmethyl)-amide
6-Benzyl-1,5,7-trioxo-1,2,3,5,6,7-hexahydro-1λ^4-thiazolo[3,2-c]pyrimidine-3-carboxylic acid benzyl ester
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methyl-benzylamide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
6-Benzyl-8-formyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide hydrochloride
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2,1,3-benzothiadiazol-5-ylmethyl)-amide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-difluoro-benzylamide
6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide
6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide hydrochloride
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-4-methoxy-benzylamide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methyl-benzylamide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-trifluoromethyl-benzylamide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-

2-carboxylic acid 4-chloro-benzylamide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-trifluoromethoxy-benzylamide
4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid sodium salt
4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester hydrochloride
4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid
4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid Sodium Salt
4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester
4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester hydrochloride
4-{8-Methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid 2-dimethylamino-ethyl ester dihydrochloride
8-Methyl-6-(2-methyl-thiazol-4-ylmethyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
2-Chloro-4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester
8-Methyl-5,7-dioxo-6-thiazol-2-ylmethyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide hydrochloride
4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-2-methyl-benzoic acid methyl ester

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-2-methoxy-benzoic acid methyl ester
6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride
6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride
6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide
8-Methyl-6-[4-(morpholine-4-carbonyl)-benzyl]-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride
{5-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-isoxazol-3-yl}-carbamic acid methyl ester
8-Methyl-5,7-dioxo-6-[4-(2H-tetrazol-5-yl)-benzyl]-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
8-Methyl-6-[4-(morpholine-4-carbonyl)-benzyl]-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
6-(6-Fluoro-quinolin-2-ylmethyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
2-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-5-methoxy-pyrimidine-4-carboxylic acid methyl ester
6-But-2-ynyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
8-Methyl-5,7-dioxo-6-(2-oxo-2H-1-benzopyran-6-ylmethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
6-(3-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-

thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride
8-Methyl-5,7-dioxo-6-(4-sulfamoyl-benzyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride
6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride
8-Methyl-5,7-dioxo-6-(2-phenylmethanesulfonyl-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
6-(E)-But-2-enyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
8-Methyl-5,7-dioxo-6-(E)-pent-2-enyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
6-sec-Butyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
8-Methyl-5,7-dioxo-6-pent-2-ynyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
8-Methyl-6-(3-methyl-but-2-enyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
6-[2-(4-Fluoro-benzenesulfonyl)-ethyl]-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
6-[3-(4-Fluoro-phenyl)-3-oxo-propyl]-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
8-Methyl-5,7-dioxo-6-(2-phenoxy-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
6-(3,4-Dichloro-benzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide
4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester
4-[2-(3-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-

thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester
4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester
6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methoxy-benzylamide

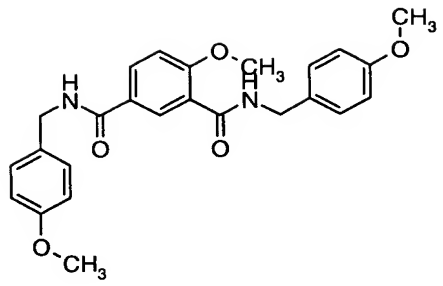
The compound of Example 1 above has first and second hydrophobic groups and first, second and third hydrogen bond acceptors. The first hydrophobic group locates in the S1' pocket of the enzyme and its hydrophobic aryl ring interacts with the aryl rings of His222 and Tyr244. The second hydrophobic group is open to solvent and forms hydrophobic interactions with the aryl rings of e.g. Phe252 and Tyr246. The three hydrogen bond acceptors interact respectively with Thr245, Thr247 and Met 253.

2. Examples of isophthalic acid allosteric inhibitors of MMP-13:

The syntheses of isophthalic acid derivatives are described in our co-pending United States nonprovisional application number 10/075,918, the corresponding PCT International application number PCT/IB02/00344, and the priority application United States provisional application number 60/268,736, filed on February 14, 2001.

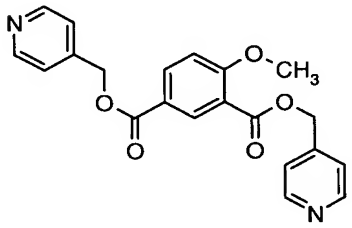
EXAMPLE 9

4-Methoxy-N,N'-bis-(4-methoxybenzyl)-isophthalamide



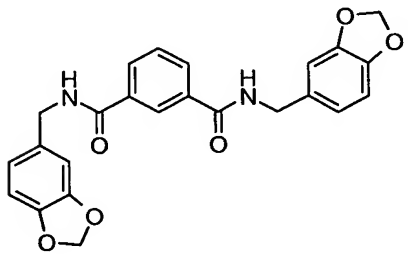
EXAMPLE 10

4-Methoxy-isophthalic acid dipyridin-4-ylmethyl ester



EXAMPLE 11

N,N-Bis-1,3-benzodioxol-5-ylmethyl-isophthalamide

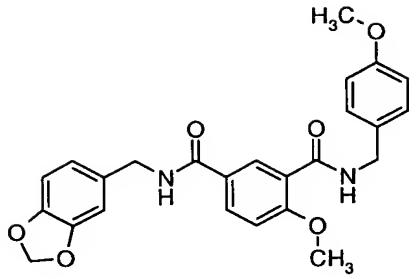


EXAMPLES 12-16

Were prepared by combinatorial synthesis.

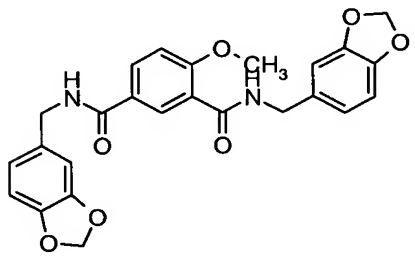
EXAMPLE 12

N-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N'-(4-methoxy-benzyl)-isophthalamide



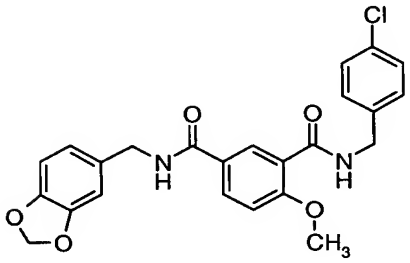
EXAMPLE 13

N,N'-Bis-1,3-benzodioxol-5-ylmethyl-4-methoxy-isophthalamide



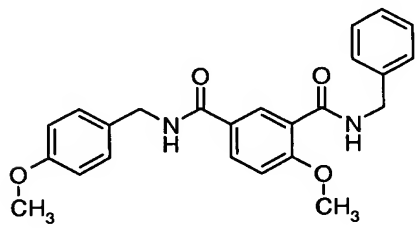
EXAMPLE 14

N-1,3-Benzodioxol-5-ylmethyl-N'-(4-chloro-benzyl)-4-methoxy-isophthalamide



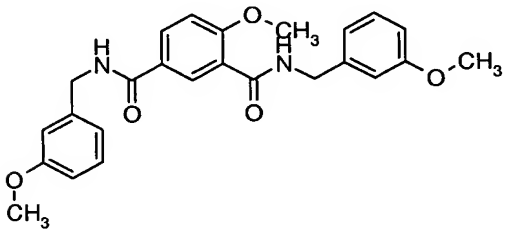
EXAMPLE 15

N-Benzyl-4-methoxy-N'-(4-methoxy-benzyl)-isophthalamide



EXAMPLE 16

4-Methoxy-N,N'-bis-(3-methoxy-benzyl)-isophthalamide



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The names of additional Examples of isophthalic acid derivatives are listed below.

4-Methoxy-N,N′-bis-(4-methoxybenzyl)-isophthalamide
N,N′-Dibenzyl-4-methoxy-isophthalamide
4-Methoxy-isophthalic acid dibenzyl ester
4-Methoxy-isophthalic acid dipyridin-4-ylmethyl ester
5-Nitro-isophthalic acid dibenzyl ester
5-Amino-isophthalic acid dibenzyl ester
Isophthalic acid bis-(4-fluoro-benzyl) ester
Isophthalic acid dibenzyl ester
N,N′-Bis-(4-chloro-benzyl)-isophthalamide
Isophthalic acid bis-(3-fluoro-benzyl) ester
Isophthalic acid bis-(4-methoxy-benzyl) ester
Isophthalic acid bis-(3-methoxy-benzyl) ester
Isophthalic acid bis-(1,3-benzodioxol-5-ylmethyl) ester
N,N′-Bis-(4-fluoro-benzyl)-isophthalamide
N,N′-Bis-(4-methoxy-benzyl)-isophthalamide
N,N′-Bis-(3-fluoro-benzyl)-isophthalamide
N,N′-Bis-(3-chloro-benzyl)-isophthalamide
N,N′-Bis-1,3-benzodioxol-5-ylmethyl-isophthalamide
4-Acetyl-isophthalic acid dibenzyl ester
4-Methoxycarbonylmethoxy-isophthalic acid dibenzyl ester

N,N′-Bis-1,3-benzodioxol-5-ylmethyl-4-methoxy-isophthalamide
N-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N′-(4-methoxy-benzyl)-isophthalamide
4-Methoxy-N,N′-bis-(4-methoxy-benzyl)-isophthalamide
N-1,3-Benzodioxol-5-ylmethyl-N′-(4-chloro-benzyl)-4-methoxy-isophthalamide
N-Benzyl-4-methoxy-N′-(4-methoxy-benzyl)-isophthalamide
N′-Benzyl-4-methoxy-N-(4-methoxy-benzyl)-isophthalamide
N,N′-Bis-1,3-benzodioxol-5-ylmethyl-isophthalamide
4-Methoxy-N-(4-methoxy-benzyl)-N′-pyridin-4-ylmethyl-isophthalamide
N,N′-Bis-(3-methoxy-benzyl)-isophthalamide
N-1,3-Benzodioxol-5-ylmethyl-N′-benzyl-isophthalamide
N-1,3-Benzodioxol-5-ylmethyl-N′-(4-methoxy-benzyl)-isophthalamide
N,N′-Dibenzyl-4-methoxy-isophthalamide
N-Benzyl-N′-(4-methoxy-benzyl)-isophthalamide
N′-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N-(2-phenoxy-ethyl)-isophthalamide
N-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N′-(2-phenoxy-ethyl)-isophthalamide
N-1,3-Benzodioxol-5-ylmethyl-N′-furan-2-ylmethyl-isophthalamide
N′-1,3-Benzodioxol-5-ylmethyl-N-(2-ethoxy-ethyl)-4-methoxy-isophthalamide
N,N′-Bis-(4-methoxy-benzyl)-isophthalamide
N,N′-Bis-(3-hydroxymethyl-phenyl)-isophthalamide
N-Benzyl-4-methoxy-N′-(2-phenoxy-ethyl)-isophthalamide
4-Methoxy-N,N′-bis-(4-methyl-benzyl)-isophthalamide
4-Methoxy-N,N′-bis-(3-methoxy-benzyl)-isophthalamide
Isophthalic acid di-(2,1,3-benzothiadiazol-5-yl)methyl ester
N-1,3-Benzodioxol-5-ylmethyl-4-methoxy-N′-(4-methoxy-benzyl)-

isophthalamide
4-Amino-N1,N3-bis-1,3-benzodioxol-5-ylmethyl-isophthalamide
4-Acetylamino-N1,N3-bis-1,3-benzodioxol-5-ylmethyl-isophthalamide
N-(3-Methoxy-benzyl)-N′-pyridin-3-ylmethyl-isophthalamide
N-(3-Methoxy-benzyl)-N′-pyridin-4-ylmethyl-isophthalamide
N1-1,3-Benzodioxol-5-ylmethyl-N3-pyridin-3-ylmethyl-isophthalamide
N-(4-Chloro-benzyl)-N′-(3-methoxy-benzyl)-isophthalamide
N-(3,4-Dichloro-benzyl)-N′-(3-methoxy-benzyl)-isophthalamide
N-(4-Methoxy-benzyl)-N′-(3-methoxy-benzyl)-isophthalamide
N-(3-Methoxy-benzyl)-N′-(4-methyl-benzyl)-isophthalamide
N,N′-Bis-(4-fluoro-3-methoxy-benzyl)-isophthalamide
({3-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-benzoyl}-benzyl-amino)-acetic acid
N-Benzo[1,3]dioxol-5-ylmethyl-isophthalamic(4-hydroxymethyl-benzoic acid) ester
N-(3,4-Dichloro-benzyl)-N′-pyridin-4-ylmethyl-isophthalamide
N-(3-Methoxy-benzyl)-N′-(4-nitro-benzyl)-isophthalamide
4-{[3-(3-Methoxy-benzylcarbamoyl)-benzoylamino]-methyl}-benzoic acid methyl ester
N-3-Methoxybenzyl-isophthalamic(4-hydroxymethyl-benzoic acid) ester
4-{[3-(3-Methoxy-benzylcarbamoyl)-benzoylamino]-methyl}-benzoic acid
N-(3-Amino-benzyl)-N′-(3-methoxy-benzyl)-isophthalamide
N-(3-Methoxy-benzyl)-N′-(3-nitro-benzyl)-isophthalamide
4-Ethoxy-N′1, N″3-bis-(3-methoxy-benzyl)-isophthalamide
N1,N3-Bis-1,3-benzodioxol-5-ylmethyl-4-ethoxy-isophthalamide
N1,N3-Bis-1,3-benzodioxol-5-ylmethyl-4-propoxy-isophthalamide
N1,N3-Bis-1,3-benzodioxol-5-ylmethyl-4-isopropoxy-isophthalamide
N1,N3-Bis-2,1,3-benzothiadiazol-5-ylmethyl-4-methoxy-isophthalamide
4-Methoxy-isophthalic acid di-2,1,3-benzothiadiazol-5-ylmethyl ester

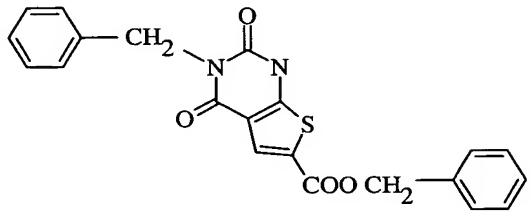
Binding of a representative example of one of the isophthalic acid derivatives is as described above for Example 1. It will be observed that the compounds of this series have two hydrophobic groups and two hydrogen bond acceptors.

3. Examples of fused bicyclic pyrimidone allosteric inhibitors of MMP-13:

The syntheses of fused bicyclic pyrimidone allosteric inhibitors of MMP-13 are described in co-pending United States nonprovisional application number 10/075,073, the corresponding PCT International application number PCT/IB02/00204, and the priority application United States provisional application number 60/268,756, filed on February 14, 2001.

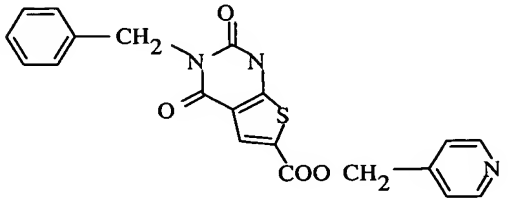
EXAMPLE 17

3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid benzyl ester



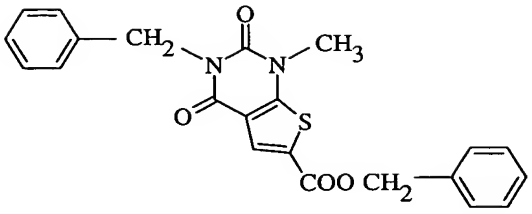
EXAMPLE 18

3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid pyridin-4-ylmethyl ester



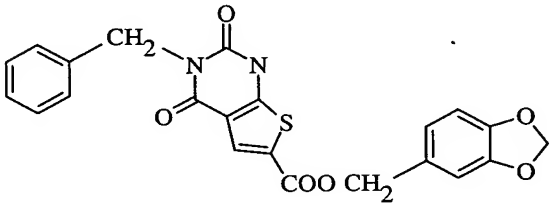
EXAMPLE 19

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid benzyl ester



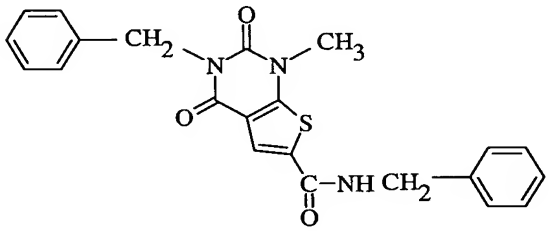
EXAMPLE 20

3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester



EXAMPLE 21

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl amide



Examples of other fused bicyclic pyrimidones are named, or their structures are drawn, below.

3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid benzyl ester
3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid pyridin-4-ylmethyl ester
5-Methyl-2,4-dioxo-3-p-tolyl-1,2,3,4-tetrahydro-thieno[2,3-d]-6-carboxylic acid benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid benzyl ester
3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-

6-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl amide
3-Benzyl-2, 4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid furfuryl-(5-carboxaldelhyde) ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid benzofuran-2-ylmethyl ester
3-(4-Bromo-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid pyridin-4-ylmethyl ester
3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzyl ester
4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-thieno[2,3-*d*]pyrimidin-3-ylmethyl}-benzoic acid; compound with trifluoro-acetic acid
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid
4-[6-(3,4-Dimethoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid
4-[6-(4-Bromo-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid
4-[6-(3,5-Bis-trifluoromethyl-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid
4-[6-(4-Chloro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid
4-[1-Methyl-2,4-dioxo-6-(4-sulfamoyl-benzylcarbamoyl)-1,4-dihydro-2H-thieno[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid
3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-

thieno[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
5-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-*d*]pyrimidin-3-ylmethyl]-furan-2-carboxylic acid ethyl ester
3-(4-Cyano-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid 3-methoxy-benzyl ester
2,4-Dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid 3-methoxy-benzyl ester

4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester
3-Cylcohexylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid-3methoxy-benzylamide
3-cylcohexylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-*d*]pyrimidine-6-carboxylic acid-4methoxy-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide
4-[6-(3-Difluoromethoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid
4-[6-(3-Difluoromethoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid tert-butyl ester
4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid
4-[6-(4-Methanesulfonyl-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid
4-[1-Methyl-2,4-dioxo-6-(2-pyridin-4-yl-ethylcarbamoyl)-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid
1-Methyl-2,4-dioxo-3-(4-trifluoromethoxy-benzyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid methyl ester
3-(2,3-Dihydro-benzofuran-6-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
1-Methyl-3-(2-methyl-thiazol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-[4-(1H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-

thieno[2,3-d]pyrimidine-6-carboxylic acid 4-fluoro-benzylamide
3-Benzyl-2-methoxy-4-oxo-3,4-dihydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid 2,2-dimethyl-propionyloxymethyl ester
4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-cyclohexanecarboxylic acid
4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-cyclohexanecarboxylic acid methyl ester
1-{4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid methyl ester
1-{4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid *tert*-butyl ester
1-{4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid
2-{4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-phenoxy}-2-methyl-propionic acid tert-butyl ester
2-{4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-phenoxy}-2-methyl-propionic acid
3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Biphenyl-4-ylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester

3-(4-Methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-3-(4-methyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(4-Amino-6-phenylamino-1,3,5-triazin-2-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-(4-trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(6-Cyano-hexyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-[2-(2,5-Dimethoxy-phenyl)-2-oxo-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-(3-trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(2,4-Bis-trifluoromethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(2-Carboxy-allyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-3-oxiranylmethyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-

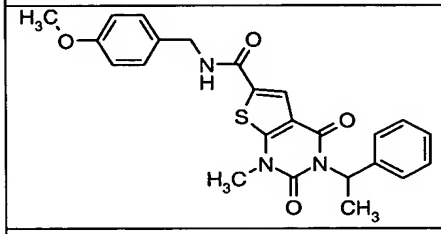
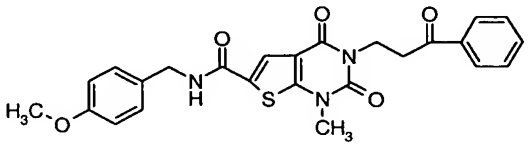
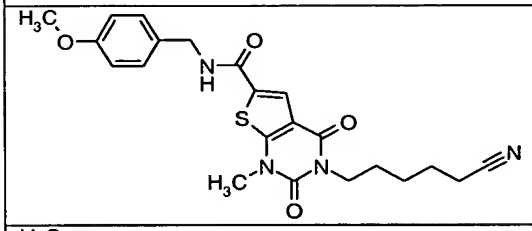
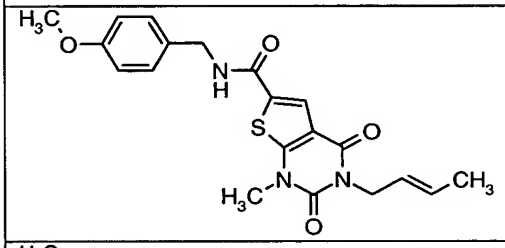
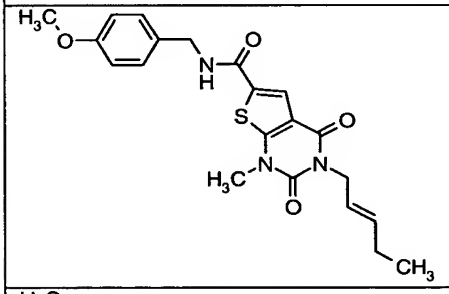
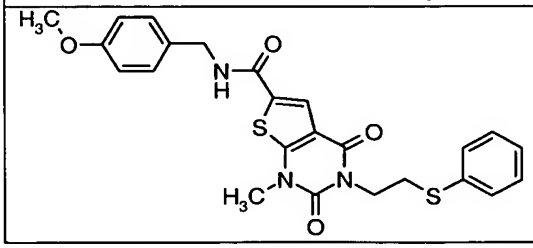
d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-3-(2-methyl-butyl)-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-(4-phenoxy-butyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(2-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-(3-phenoxy-propyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Hex-5-enyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-pyridin-3-ylmethyl-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Cyclobutylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Allyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-prop-2-ynyl-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-But-2-ynyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-(2-phenoxy-ethyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(3-Hydroxy-2-methyl-propyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Isobutyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(6-Chloro-pyridin-3-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester

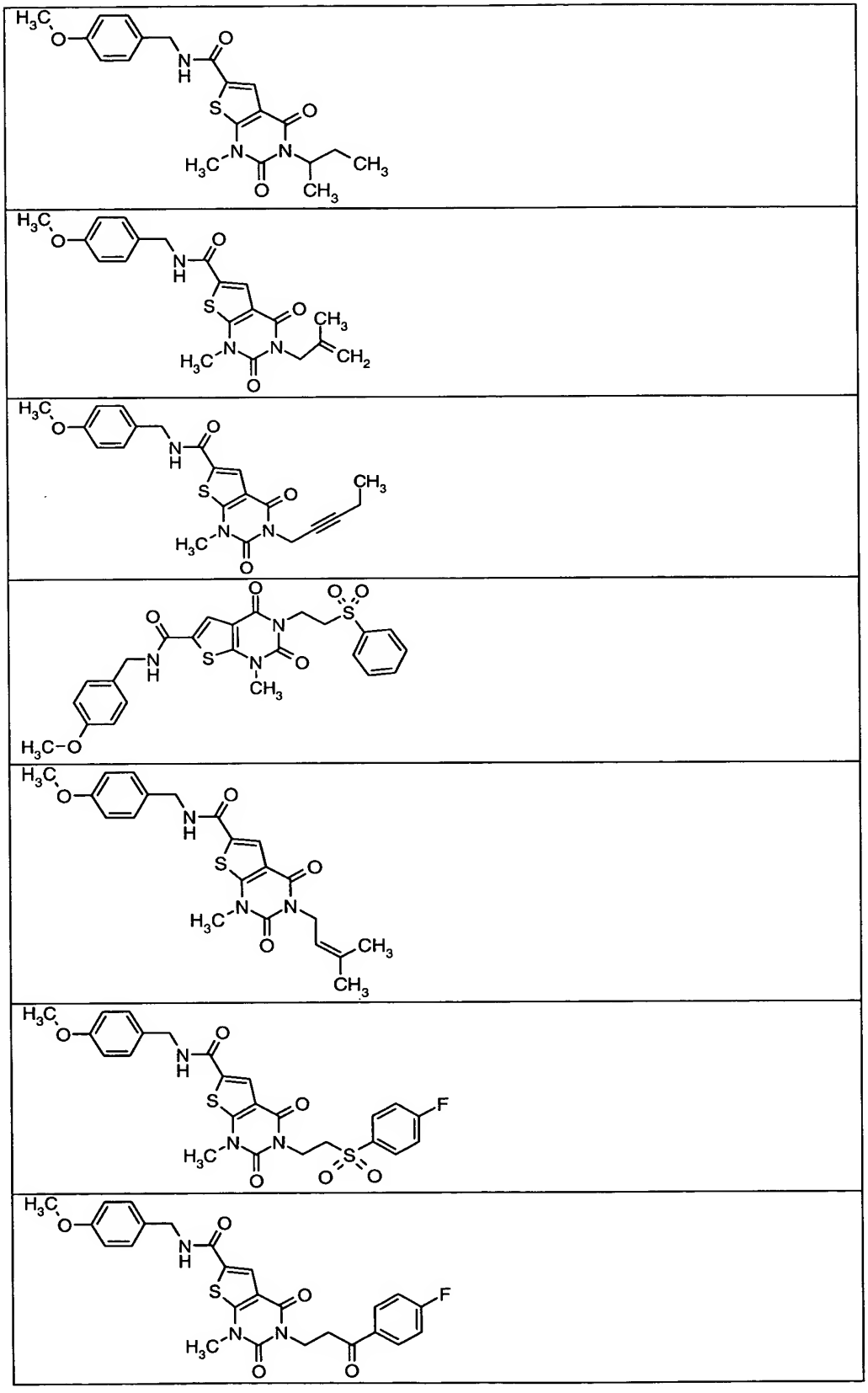
3-(2-Benzenesulfonylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-3-naphthalen-1-ylmethyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-(2-trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(4-Methoxycarbonyl-butyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Ethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-(3-phenyl-propyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-[2-(4-Chloro-benzenesulfonyl)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(2-Acetoxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl amide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 2-diethylamino-1-methyl-ethyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-fluoro-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-trifluoromethyl-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid pyridin-3-ylmethyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-

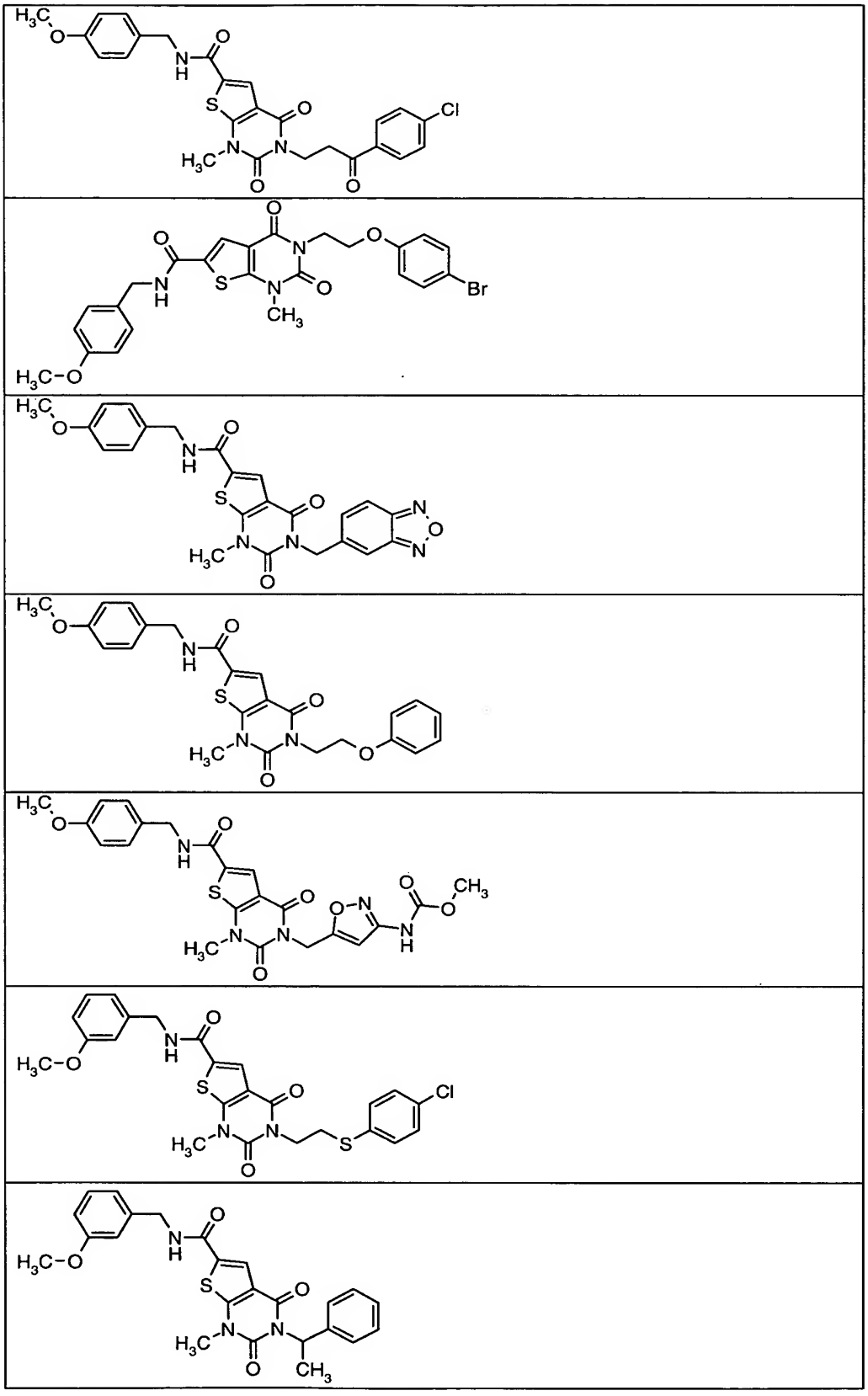
6-carboxylic acid 4-methoxy-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 2-benzyloxy-ethyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-nitro-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-phenoxy-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-chloro-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 1-ethyl-piperidin-3-yl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-(4-methoxy-phenyl)-propyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid tetrahydro-furan-3-yl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-chloro-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 1,3-benzodioxol-5-ylmethyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methylsulfanyl-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3,4-dichloro-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid furan-3-ylmethyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid but-3-enyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 2-ethoxy-ethyl ester

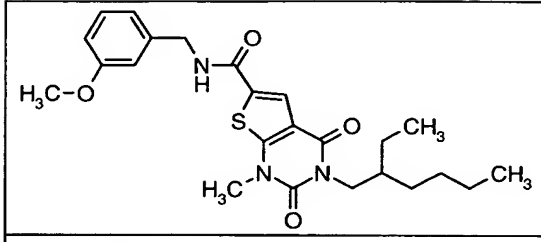
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid cyano-phenyl-methyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-trifluoromethyl-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methyl-benzylamide
1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-[4-(N-Hydroxycarbamimidoyl)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-[4-(5-thioxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-Cyanomethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
(E)-4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-yl]-but-2-enoic acid methyl ester
2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid methyl ester
3-(2-Methoxymethyl-1,1,3-trioxo-2,3-dihydro-1H-1λ^6-1,2-benzisothiazol-6-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-oct-2-ynyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide

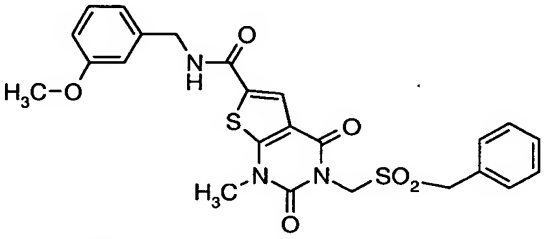
3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-[2-(4-fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
3-[2-(4-chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-2-methyl-benzoic acid methyl ester
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid methyl ester
2-Methoxy-4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid methyl ester
4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl]-2-methyl-benzoic acid methyl ester
1-Methyl-2,4-dioxo-3-(3-oxo-3-phenyl-propyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-(3-oxo-3-phenyl-propyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-[2-(3-trifluoromethyl-benzenesulfonyl)-ethyl]-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
3-[2-(4-Chloro-benzenesulfonyl)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
3-[2-(4-Chloro-benzenesulfonyl)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
4-[6-(3-hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-

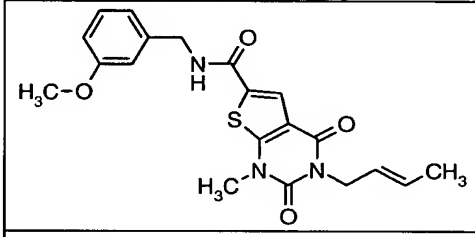
thieno[2,3-d]pyrimidin-3-ylmethyl]-2-methyl-benzoic acid
4-(6-Carbamoyl-1-methyl-2,4-dioxo-1,4-dihydro-2H-thieno[2,3-d]pyrimidin-3-ylmethyl)-2-hydroxy-benzoic acid







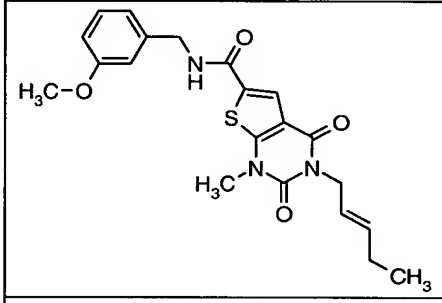


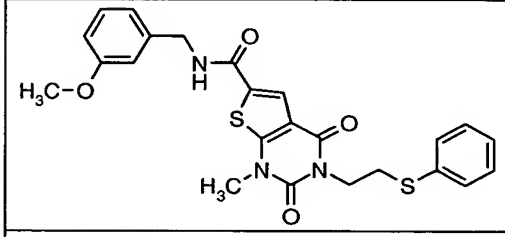


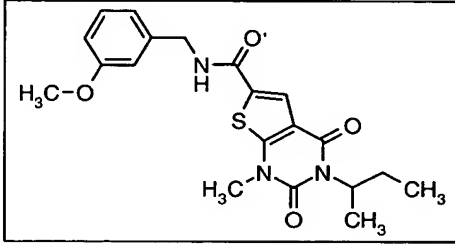


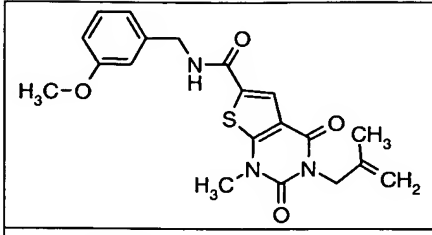
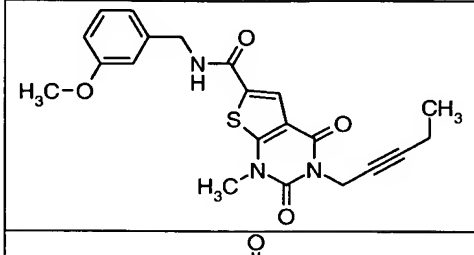
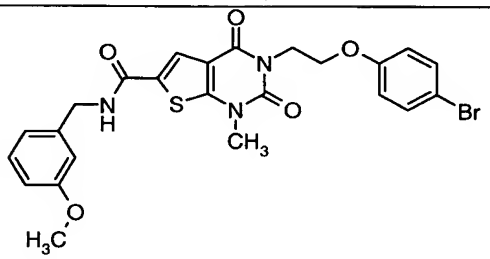
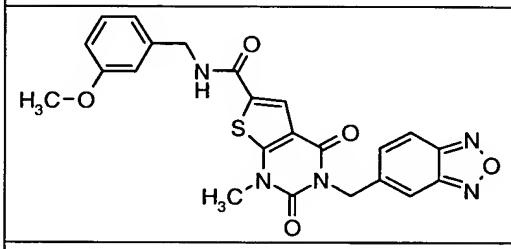
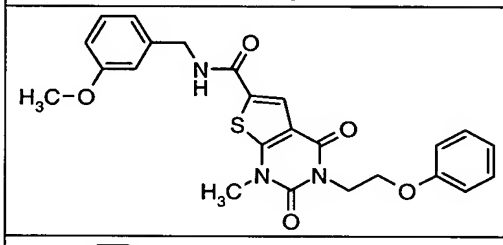
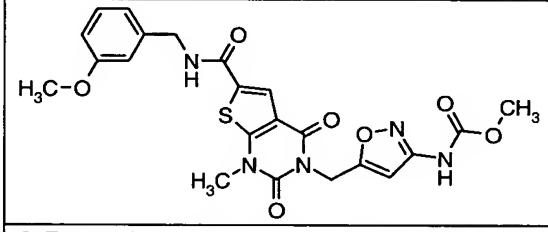
















3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid pyridin-4-ylmethyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzo[b]thiophen-2-ylmethyl ester
3-(1,3-Benzodioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-

thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-pyridin-4-ylmethyl-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(4-*tert*-Butyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-2,4-dioxo-3-(4-trifluoromethoxy-benzyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
1-Methyl-3-naphthalen-2-ylmethyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzofuran-5-ylmethyl ester
3-(3,5-Dimethoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid benzyl ester
3-(4-Carboxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 2-ethoxy-benzyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid [2-(3-ethoxy-phenyl)-ethyl]-amide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-chloro-4-fluoro-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-chloro-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-trifluoromethyl-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-

6-carboxylic acid 3-methoxy-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid (thiophen-2-ylmethyl)-amide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid (5-methyl-furan-2-ylmethyl)-amide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-bromo-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid [2-(1H-indol-3-yl)-ethyl]-amide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 2,4-dimethoxy-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-chloro-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3,4-dichloro-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-fluoro-3-trifluoromethyl-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid (2-pyridin-2-yl-ethyl)-amide
3-Cyanomethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Cyclopropylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
1-Methyl-3-(6-nitro-pyridin-3-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
1-Methyl-3-(6-nitro-pyridin-3-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-(6-nitro-pyridin-3-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

3-Cyclohexylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
3-(6-Amino-pyridin-3-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-(3-phenyl-prop-2-ynyl)-1,2,3,4-tetrahydro-thieno[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide

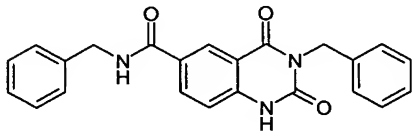
Binding of a representative compound of the fused bicyclic pyrimidone allosteric inhibitors of MMP-13 is through two hydrophobic groups and three hydrogen bond acceptors, the third hydrogen bond acceptor binding to Met 253 and also via a bridging water molecule to the backbone carbonyl of His251.

4. Examples of substituted quinazoline allosteric inhibitors of MMP-13:

The syntheses of quinazoline allosteric inhibitors of MMP-13 are described in our co-pending United States nonprovisional application number 10/075,954, the related PCT International application number PCT/EP02/01979, and the corresponding priority United States provisional application number 60/268,661, filed on February 14, 2001.

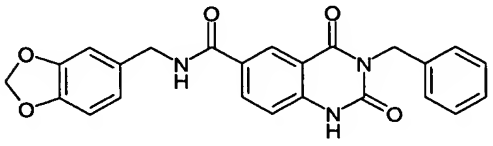
EXAMPLE 22

3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide



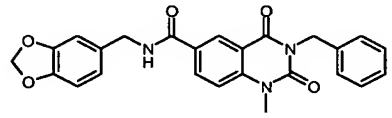
EXAMPLE 23

3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



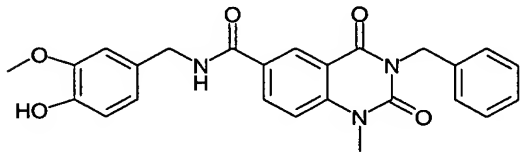
EXAMPLE 24

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



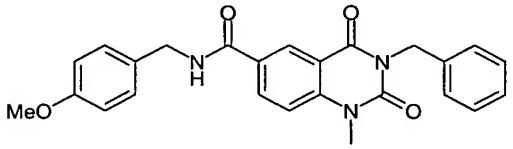
Example 25

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-hydroxy-3-methoxybenzylamide



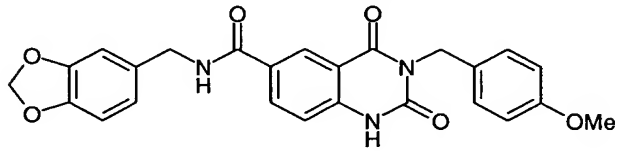
EXAMPLE 26

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide



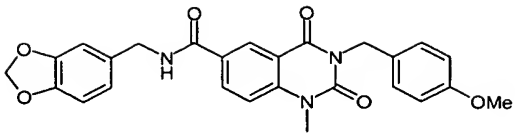
EXAMPLE 27

3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



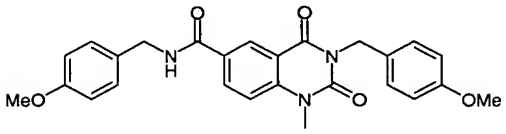
EXAMPLE 28

3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



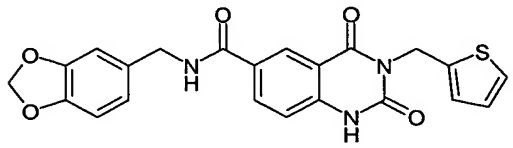
EXAMPLE 29

3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide



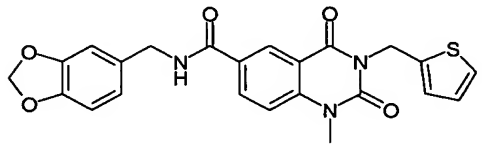
EXAMPLE 30

2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



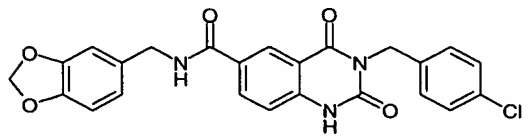
EXAMPLE 31

1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



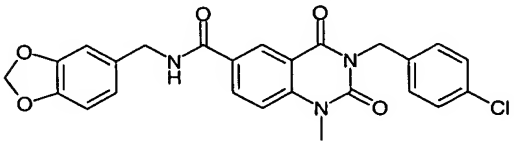
EXAMPLE 32

3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



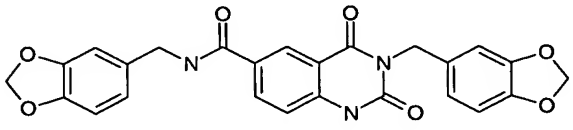
EXAMPLE 33

3-(4-Chlorobenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



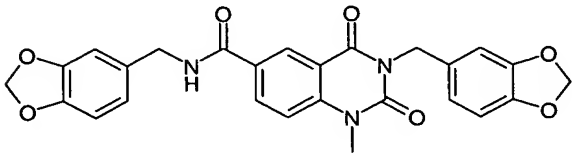
EXAMPLE 34

3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



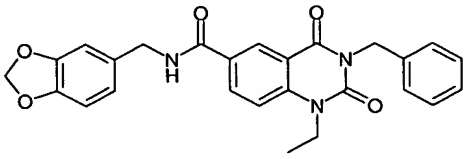
EXAMPLE 35

3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



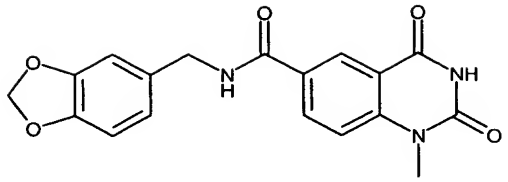
EXAMPLE 36

3-Benzyl-1-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



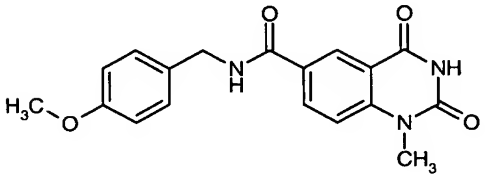
EXAMPLE 37

1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

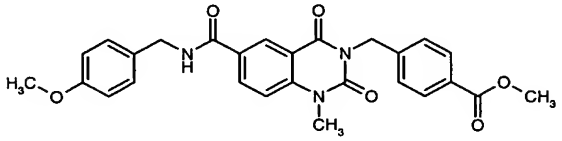


EXAMPLE 38

38a: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide:

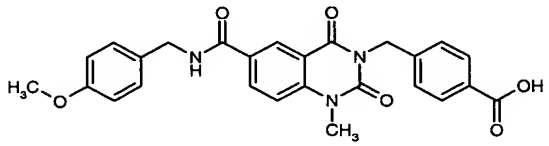


38b: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid methyl ester



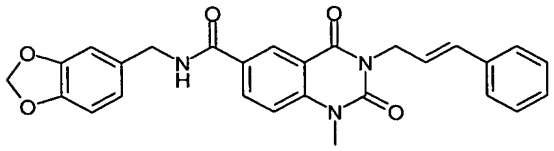
EXAMPLE 39

4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H]-quinazolin-3-ylmethyl]-benzoic acid



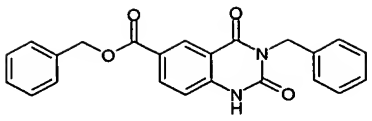
EXAMPLE 40

1-Methyl-2,4-dioxo-3-((E)-3-phenylallyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide



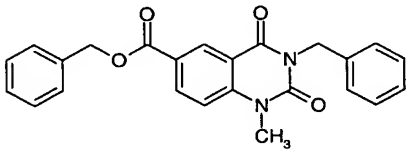
EXAMPLE 41

Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate



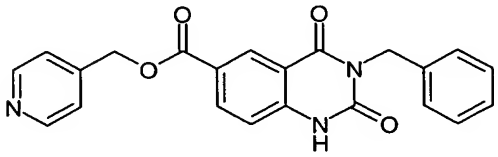
EXAMPLE 42

Benzyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate



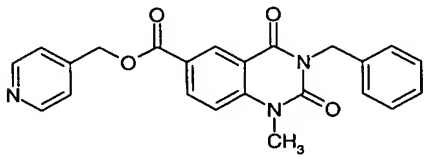
EXAMPLE 43

4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate



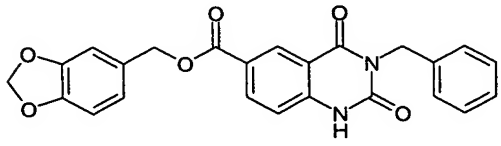
EXAMPLE 44

4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate



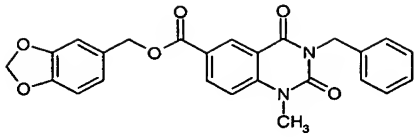
EXAMPLE 45

Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate



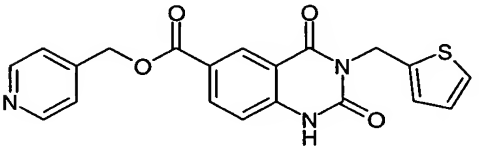
EXAMPLE 46

Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate



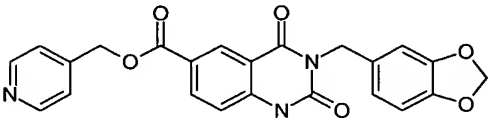
EXAMPLE 47

4-Pyridylmethyl 2,4-dioxo-3-thien-2-ylmethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylate



EXAMPLE 48

4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydro quinazoline-6-carboxylate



The names of other Examples of quinazoline allosteric inhibitors of MMP-13 are listed below.

3-Benzyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide
4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-Allyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-(2-pyrrol-1-yl-ethyl)-1,2,3,4-tetrahydro-quinazoline-6- carboxylic acid 4-methoxy-benzylamide

1-Methyl-2,4-dioxo-3-prop-2-ynyl-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-(3-methyl-but-2-enyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6- carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-Carbamoylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
1-Methyl-2,4-dioxo-3-pyridin-3-ylmethyl-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-(1-methyl-piperidin-3-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(3-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(2-Methoxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-Cyclopropylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-(2-morpholin-4-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-Cyclohexylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-(3-phenyl-propyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

3-[2-(4-Diethylamino-phenyl)-2-oxo-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
Ethyl [6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*- quinazolin-3-yl]-acetate
3-(2-Hydroxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
Methyl 3-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-propionate
3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-propionic acid
Ethyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*- quinazolin-3-yl]-butyrate
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-butyric acid
Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-acetate
{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-acetic acid
3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-3-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-4-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydroquinazoline-6- carboxylic acid 4-methoxy-benzylamide
3-(4-Methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-[4-(2-Dimethylamino-ethylsulfamoyl)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
Methyl 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
(E) Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-but-2-enoate
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-but-2-enoic acid
Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-furan-2-carboxylate
5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-furan-2-carboxylic acid
Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-thiophene-2-carboxylate
5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-thiophene-2-carboxylic acid
1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Dimethylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

3-[4-(*N,N*-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-Benzofurazan-5-ylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-[2-(4-Fluorophenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(2-Benzenesulfonyl-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamine
1-Methyl-2,4-dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
Methyl 2-chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
2-Chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
1-Methyl-3-[4-(1-methyl-1*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-3-[4-(2-methyl-2*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
Methyl 2-methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate

2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
1-Methyl-2,4-dioxo-3-(pyridin-4-methyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide
1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6- carboxylic acid 4-hydroxy-benzylamide
Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
Methyl 4-[1-methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
4-[1-Methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
Methyl 4-[1-ethyl-2,4-dioxo-6-(4-trifluoromethoxy-benzylcarbamoyl)-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*- quinazolin-3-ylmethyl]-benzoate
4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
Methyl 4-{6-[(benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate

4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid
Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
Methyl 4-[1-ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*- quinazolin-3-ylmethyl]-benzoate
4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
3-(4-Hydroxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
1-Methyl-2,4-dioxo-3-(3-pyridin-4-yl-allyl)-1,2,3,4-tetrahydro-quinazoline-6- carboxylic acid (pyridin-4-ylmethyl)-amide
Methyl 4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate
4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*- quinazolin-3-ylmethyl}-benzoic acid
Methyl (4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-phenyl)-acetate
(4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2*H*- quinazolin-3-ylmethyl}-phenyl)-acetic acid
Methyl 4-{1-methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)carbamoyl]-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate

Methyl{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-1-yl}-acetate
{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-3,4-dihydro-2*H*-quinazolin-1-yl}-acetic acid,
Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro -2*H*-quinazolin-3-ylmethyl}-benzoate
4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid [3-(pyridin-4-ylsulfanyl)-propyl]-amide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-hydroxy-benzylamine
Ethyl (4-{[(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl}-phenoxy)-acetate
(4-{[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)amino]-methyl}-phenoxy)-acetic acid
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-cyano-benzylamide
3-(4-Dimethylamino-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro- quinazoline-6-carboxylic acid 4-methoxy-benzylamide
tert-Butyl {5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-pyridin-2-yl}-carbamate
3-(6-Amino-pyridin-3-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide
1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*] pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[2,3-*d*] pyrimidin-3-ylmethyl]-benzoic acid
3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*] pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*] pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide
Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*] pyrimidin-3-ylmethyl]-benzoic acid
4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*] pyrimidin-3-ylmethyl]-benzoic acid
3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
3-Benzyl-1-methyl-6-(3-phenyl-propionyl)-1H-quinazoline-2,4-dione
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-4-yl-allyl ester
3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-3-yl-allyl ester
3-Benzyl-1-methyl-6-[2-(pyridin-4-ylsulfanyl)-acetyl]-1*H*-quinazoline-2,4-dione

3-(4-Aminomethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
1-Methyl-2,4-dioxo-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
Methyl 4'-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-biphenyl-2-carboxylate
4'-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-biphenyl-2-carboxylic acid
Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate
2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid
2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-2-methyl-benzoic acid 2-dimethylamino-ethyl ester
1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl]-phenyl}-acetic acid
1-Methyl-3-(1-naphthalen-1-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide
3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide
1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide
3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6- carboxylic acid (pyridin-3-ylmethyl)-amide
3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6- carboxylic acid (pyridin-4-ylmethyl)-amide
3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6- carboxylic acid 4-methoxy-benzylamide
3-(3-chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate(2-hydroxy-ethyl)-trimethyl-ammonium
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemi calcium
4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemi magnesium

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide
3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide
3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide
3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide
3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
tert-Butyl 1-{4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylate
1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-pheny1}-cyclopropanecarboxylic acid
3-Benzyl-6-benzylsulfanyl-1-methyl-1*H*-quinazoline-2,4-dione
4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid tert-butoxycarbonylmethyl ester
4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid dimethylamino-dimethyl-propyl ester
4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid dimethylamino-methyl-propyl ester
4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid 2-dimethylamino-ethyl ester

4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]- benzoic acid 2-(2-amino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester

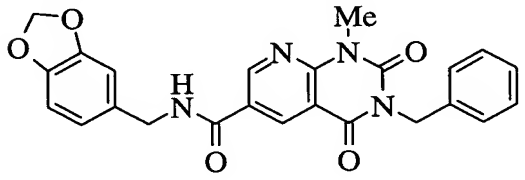
Binding of the compound of Example 35 is based on two hydrophobic groups and three hydrogen bond acceptors. As in the thiazolopyrimidinediones, the third hydrogen bond acceptor binds both to Met 253 and via a bridging water molecule to the backbone carbonyl oxygen of His 251. It will also be noted from the above table that some compounds in this series do not have a second hydrophobic group, but nevertheless bind to MMP-13 and exhibit a useful inhibitory activity.

5. Examples of pyrido[2,3-*d*]pyrimidines:

The syntheses of pyrido[2,3-*d*]pyrimidine allosteric inhibitors of MMP-13 are also described in our co-pending United States nonprovisional application number 10/075,954, the related PCT International application number PCT/EP02/01979, and the corresponding priority United States provisional application number 60/268,661, filed on February 14, 2001.

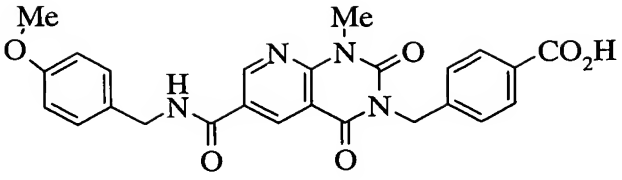
EXAMPLE 49

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide



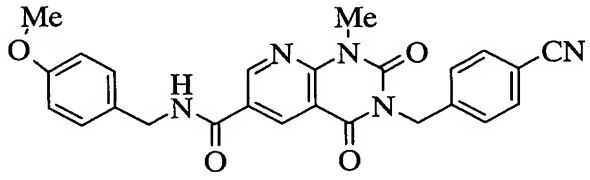
EXAMPLE 50

4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-ylmethyl]-benzoic acid



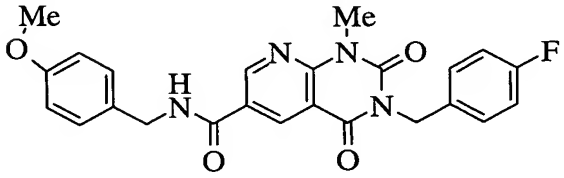
EXAMPLE 51

3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*] pyrimidine-6-carboxylic acid 4-methoxy-benzylamide



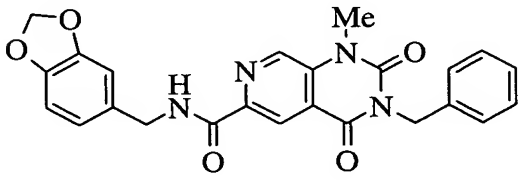
EXAMPLE 52

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*] pyrimidine-6-carboxylic acid 4-methoxy-benzylamide



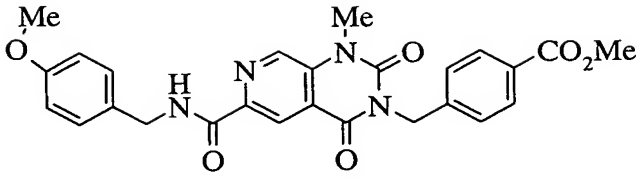
EXAMPLE 53

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide



EXAMPLE 54

Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate

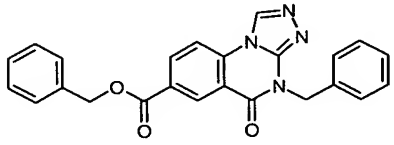


6. Examples of fused triazolo-quinazoline allosteric inhibitors of MMP-13:

Syntheses of fused triazolo-quinazoline allosteric inhibitors of MMP-13 are described in our co-pending United States nonprovisional application number 10/075,654, the related PCT International application number PCT/FR02/00504, and the priority application United States provisional application number 60/268,757, filed on February 14, 2001.

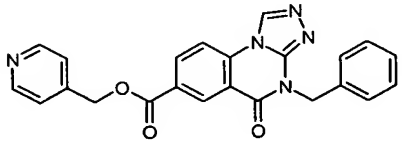
EXAMPLE 55

Benzyl 4-benzyl-5-oxo-4*H*-[1,2,4]triazolo[4,3-*a*]quinazol-7-ylcarboxylate



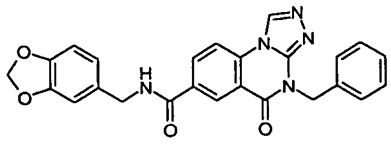
EXAMPLE 56

4-Pyridylmethyl 4-benzyl-5-oxo-4*H*-[1,2,4]triazolo[4,3-*a*]quinazol-7-yl-carboxylate



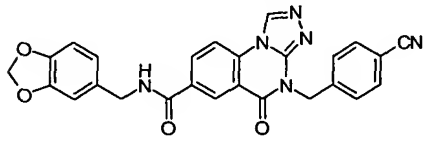
EXAMPLE 57

N-(3,4-Methylenedioxybenzyl)-4-benzyl-5-oxo-4*H*-[1,2,4]triazolo[4,3-*a*]-quinazol-7-ylcarboxamide



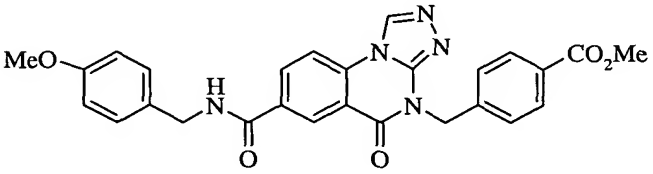
EXAMPLE 58

N-(3,4-Methylenedioxybenzyl)-4-(4-cyanobenzyl)-5-oxo-4*H*-[1,2,4]triazolo [4,3-*a*]quinazol-7-ylcarboxamide



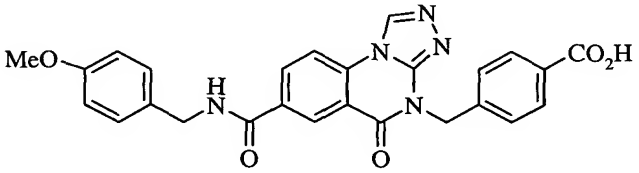
EXAMPLE 59

Methyl 4-{7-[(4-methoxybenzyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazol-4-ylmethyl} benzoate



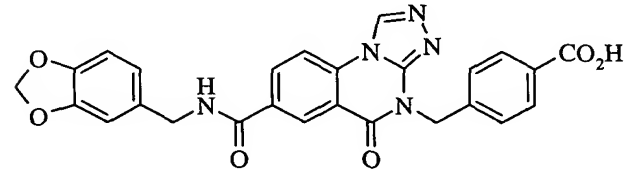
EXAMPLE 60

4-{7-[(4-Methoxybenzyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*]quinazol-4-ylmethyl} benzoic acid



EXAMPLE 61

4-{7-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazol-4-ylmethyl} benzoic acid



Additional Examples of fused triazolo-quinazoline allosteric inhibitors of MMP-13 are named below.

4-Benzyl-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid benzyl ester;

4-Benzyl-5-oxo-4,5-dihydro- [1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid pyridin-4-ylmethyl ester;

4-Benzyl-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;

4-Benzyl-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid (pyridin-4-ylmethyl)-amide;

4-Benzyl-5-oxo-4,5-dihydro-imidazo[1,2-a]quinazoline-7-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;

4-Benzyl-5-oxo-4,5-dihydro-imidazo[1,2-a]quinazoline-7-carboxylic acid (pyridin-4-ylmethyl)-amide;

N-(4-Methoxybenzyl)-4-benzyl-5-oxo-4,5-dihydro[1,2,4]triazolo [4,3-*a*]quinazoline-7-carboxamide;

N-[3-(4-Pyridylsulphanyl) propyl]-4-benzyl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*] quinazoline-7-carboxamide;

N-(3,4-Methylenedioxybenzyl)-4-(4-cyanobenzyl)-5-oxo-4*H*-[1,2,4]triazolo[4,3-*a*] quinazol-7-ylcarboxamide;

Methyl 4-{7-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazol-4-ylmethyl} benzoate;

Methyl 4-{7-[(4-methoxy benzyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazol-4-ylmethyl} benzoate;

Methyl 4-{7-[(pyridin-4-ylmethyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazol-4-ylmethyl} benzoate;

(2-Dimethylamino-ethyl) 4-[7-(4-fluoro-benzylcarbamoyl)-5-oxo-5*H*-[1,2,4]triazolo [4,3-*a*] quinazol-4-ylmethyl] benzoate;

4-(4-Dimethylcarbamoyl-benzyl)-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazoline-7-carboxylic acid 4-methoxy-benzylamide;

N-(pyridin-4ylmethyl)-4-(4-cyanobenzyl)-5-oxo-4*H*-[1,2,4]triazolo[4,3-*a*]quinazol-7-ylcarboxamide;

Methyl (4-{7-[(1,3-benzodioxol -5-ylmethyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-4-ylmethyl}-phenyl)-acetate;

Methyl (4-{7-[(4-methoxy)-benzylcarbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-4-ylmethyl}-phenyl)-acetate;

Methyl (4-{7-[(pyridin-4-yl)-methylcarbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-4-ylmethyl}-phenyl)-acetate;

N-(pyridin-4-ylmethyl) 4-[3-(pyridin-4-yl)-2-propen-1-yl]-5-oxo-4*H*-[1,2,4]triazolo[4,3-*a*] quinazol-7-ylcarboxamide;

4-[2-(4-Chloro-phenoxy)-ethyl]-5-oxo-4,5-dihydro-[1,2,4] triazolo[4,3-a]quinazoline-7-carboxylic acid 4-methoxy-benzylamide;

4-{7-[(4-Methoxybenzyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*]quinazol-4-ylmethyl} benzoic acid;

4-{7-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazol-4-ylmethyl} benzoic acid;

4-{7-[(Pyridin-4-ylmethyl)-carbamoyl]-5-oxo-5*H*-[1,2,4] triazolo[4,3-*a*]quinazol-4-ylmethyl} benzoic acid;

4-{7-[(4-Fluoro)-benzyl carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*]quinazol-4-ylmethyl} benzoic acid;

(4-{7-[(4-Methoxy)-benzyl carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-4-ylmethyl}-phenyl)-acetic acid;

(4-{7-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-4-ylmethyl}-phenyl)-acetic acid; and

(4-{7-[(Pyridin-4-yl)-methylcarbamoyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-4-ylmethyl}-phenyl)-acetic acid.

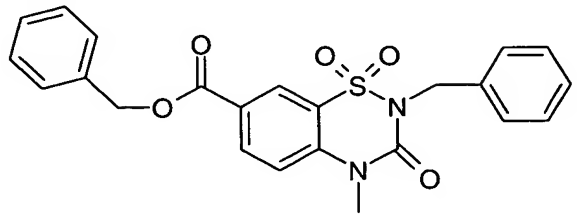
Binding of a representative compound in the fused triazolo-quinazoline, Example 57 involves first and second hydrophobic groups and first, second and third hydrogen bond acceptors.

7. Examples of 1,1-dioxy-benzo-(1,2,4)-thiadiazine allosteric inhibitors of MMP-13:

The syntheses of 1,1-dioxy-benzo-(1,2,4)-thiadiazine allosteric inhibitors of MMP-13 are described in our co-pending United States nonprovisional application number 10/074,646, the related PCT International application number PCT/IB02/00083, and the priority application United States provisional application number 60/268,782, filed on February 14, 2001.

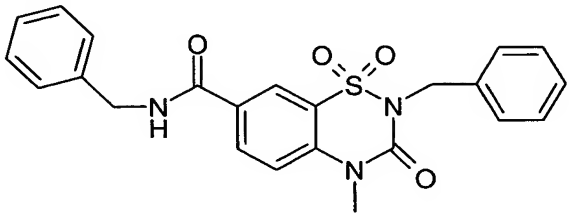
EXAMPLE 62

2-Benzyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine -7-carboxylic acid benzyl ester



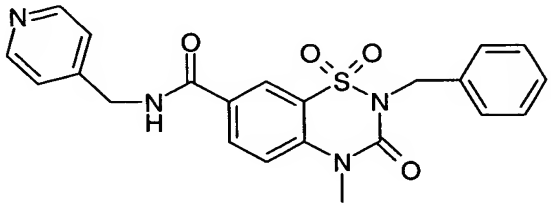
EXAMPLE 63

2-Benzyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine -7-carboxylic acid benzylamide



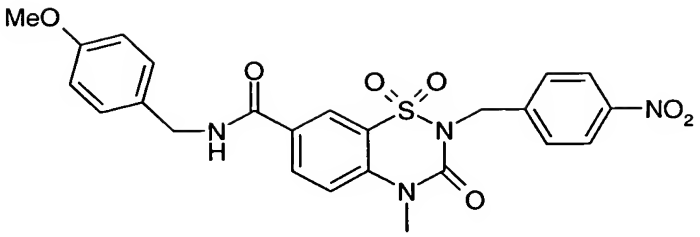
EXAMPLE 64

2-Benzyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine -7-carboxylic acid (pyridin-4-ylmethyl)-amide



EXAMPLE 65

4-Methyl-2-(4-nitro-benzyl)-1,1,3-trioxo-1,2,3,4-tetrahydro-1 λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide



The names of other Examples of 1,1-dioxy-benzo-(1,2,4)-thiadiazine allosteric inhibitors of MMP-13 are listed below.

2-Benzyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
4-(7-Benzylcarbamoyl-4-methyl-1,1,3-trioxo-3,4-dihydro-*H*-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl)-benzoic acid
4-[7-(4-Methoxy-benzylcarbamoyl)-4-methyl-1,1,3-trioxo-3,4-dihydro-1*H*-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid
2-(4-Carbamoyl-benzyl)-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
2-Benzyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-fluoro-benzylamide
4-Methyl-2-(4-methylsulfamoyl-benzyl)-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
4-Methyl-2-[4-(morpholine-4-sulfonyl)-benzyl]-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
4-[7-(4-Fluoro-benzylcarbamoyl)-4-methyl-1,1,3-trioxo-3,4-dihydro-1*H*-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid methyl ester
2-Benzyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
4-Methyl-2-naphthalen-2-ylmethyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide

2-Benzyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid (2,1,3-benzothiadiazol-5-ylmethyl)-amide
4-[7-(4-Fluoro-benzylcarbamoyl)-4-methyl-1,1,3-trioxo-3,4-dihydro-1*H*-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid
4-[7-(4-Methoxy-benzylcarbamoyl)-4-methyl-1,1,3-trioxo-3,4-dihydro-1*H*-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester hydrochloride
4-Methyl-1,1,3-trioxo-2-[4-(piperidine-1-carbonyl)-benzyl]-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine -7-carboxylic acid 4-methoxy-benzylamide
2-{4-[7-(4-Methoxy-benzylcarbamoyl)-4-methyl-1,1,3-trioxo-3,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoylamino}-3-methyl-butyric acid
{4-[7-(4-Methoxy-benzylcarbamoyl)-4-methyl-1,1,3-trioxo-3,4-dihydro-1*H*-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-phenyl}-acetic acid
2-(4-cyano-benzyl)-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine -7-carboxylic acid 4-methoxy-benzylamide
4-[7-(3-Methoxy-benzylcarbamoyl)-4-methyl-1,1,3-trioxo-3,4-dihydro-1*H*-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid
4-Methyl-1,1,3-trioxo-2-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
2-Benzyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 3-methoxy-benzylamide
4-methyl-1,1,3-trioxo-2-pent-2-ynyl-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
4-Methyl-1,1,3-trioxo-2-(1-phenyl-ethyl)-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide

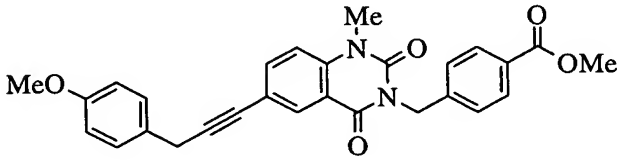
2-(5-Cyano-pentyl)-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
2-(E)-But-2-enyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
4-Methyl-1,1,3-trioxo-2-(E)-pent-2-enyl-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
4-Methyl-2-(2-methyl-allyl)-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
4-Methyl-2-(3-methyl-but-2-enyl)-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
2-Benzo[1,2,5]oxadiazol-5-ylmethyl-4-methyl-1,1,3-trioxo-1,2,3,4-tetrahydro-1λ^6-benzo[1,2,4]thiadiazine-7-carboxylic acid 4-methoxy-benzylamide
{5-[7-(4-Methoxy-benzylcarbamoyl)-4-methyl-1,1,3-trioxo-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-isoxazol-3-yl}-carbamic acid methyl ester

8. Examples of alkynylated quinazoline allosteric inhibitors of MMP-13:

The syntheses of alkynylated quinazoline allosteric inhibitors of MMP-13 are described in our co-pending United States provisional application number 60/329,181, and the corresponding PCT International application number PCT/EP01/11824, both filed on October 12, 2001.

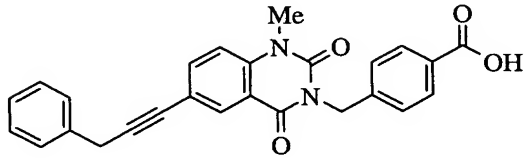
EXAMPLE 66

Methyl 4-{6-[3-(4-methoxyphenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate



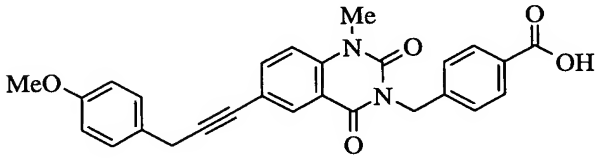
EXAMPLE 67

4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid



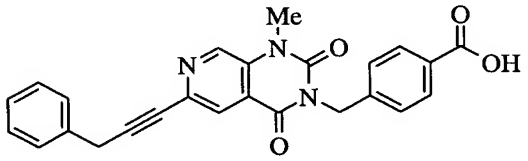
EXAMPLE 68

4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid



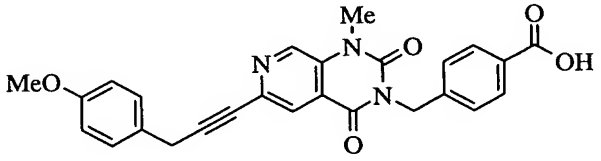
EXAMPLE 69

4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid



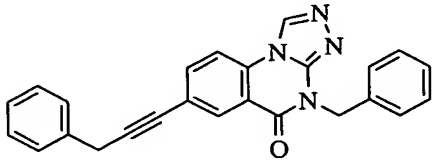
EXAMPLE 70

4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl}-benzoic acid



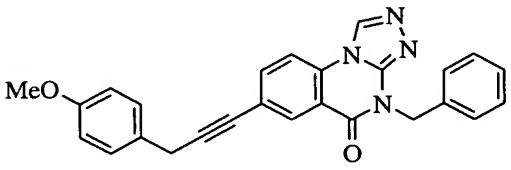
EXAMPLE 71

4-Benzyl-7-(3-phenyl-prop-1-ynyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one



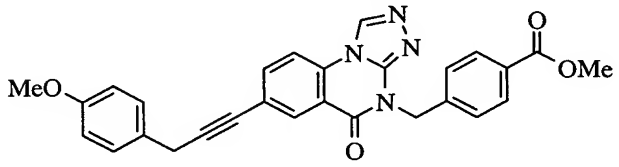
EXAMPLE 72

4-Benzyl-7-[(4-methoxyphenyl)-prop-1-ynyl]-4*H*-[1,2,4]-triazolo[4,3-*a*] quinazolin-5-one



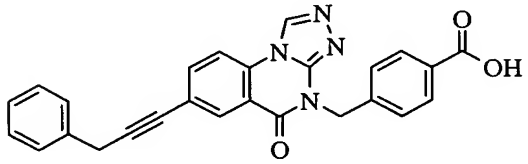
EXAMPLE 73

Methyl 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5*H*-[1,2,4]triazolo [4,3-*a*]quinazolin-4-ylmethyl}-benzoate



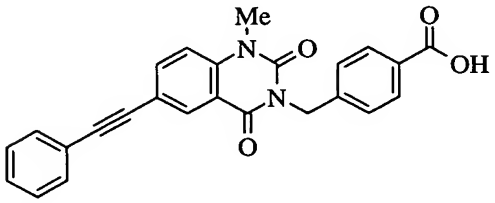
EXAMPLE 74

4-[5-Oxo-7-(3-phenyl-prop-1-ynyl)-5*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-4-ylmethyl]-benzoic acid



EXAMPLE 75

4-(1-Methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid



Representative additional Examples of alkynylated quinazoline allosteric inhibitors of MMP-13 are named below:

- methyl 4-{6-[3-(4-methoxyphenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate,
- 4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- 4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid,
- 4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid,
- 4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid,
- 4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one,
- 4-benzyl-7-[(4-methoxyphenyl)-prop-1-ynyl]-4H-[1,2,4]-triazolo[4,3-a] quinazolin-5-one,
- methyl 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo [4,3-a] quinazolin-4-ylmethyl}-benzoate,
- 4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid,
- and 4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin -3-ylmethyl)-benzoic acid.

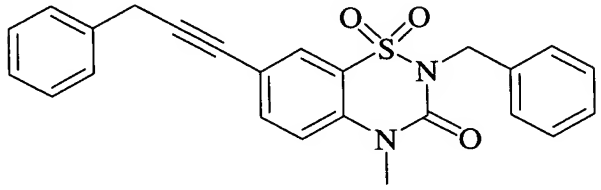
It should be appreciated that the alkyne group between the first scaffold ring and the first hydrophobic group forms part of the first hydrogen bond acceptor.

9. Examples of other allosteric alkyne inhibitors of MMP-13:

The syntheses of other allosteric alkyne inhibitors of MMP-13 are described in our co-pending United States provisional application number 60/329,216, filed on October 12, 2001.

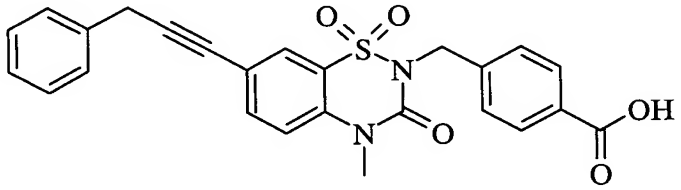
EXAMPLE 76

2-Benzyl-4-methyl-1,1-dioxo-7-(3-phenyl-prop-1ynyl)-1,4-dihydro-2H-1l^6-benzo[1,2,4]thiadiazin-3-one



EXAMPLE 77

4-[4-Methyl-1,1,3-trioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-1l^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid

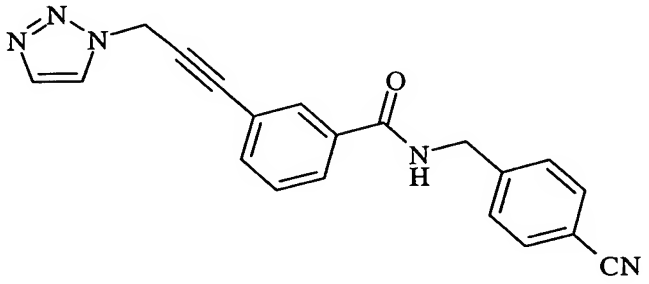


EXAMPLE 78

2-Benzyl-1,1-dioxo-7-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-1l^6-benzo[1,2,4]thiadiazin-3-one

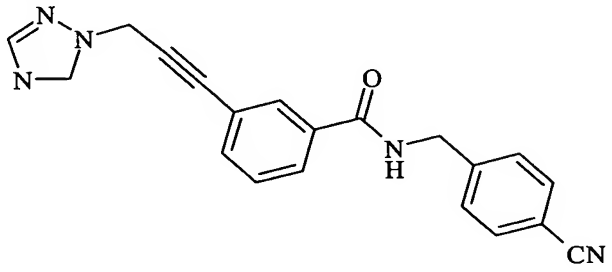
EXAMPLE 79

N-(4-Cyano-benzyl)-3-(3-[1,2,3]-triazol-1-yl-prop-1-ynyl)-benzamide



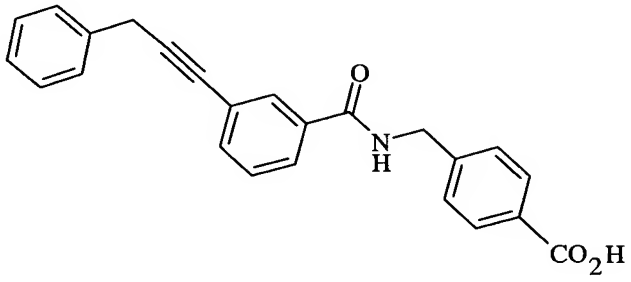
EXAMPLE 80

N-(4-Cyano-benzyl)-3-(3-[1,2,3]-triazol-1-yl-prop-1-ynyl)-benzamide



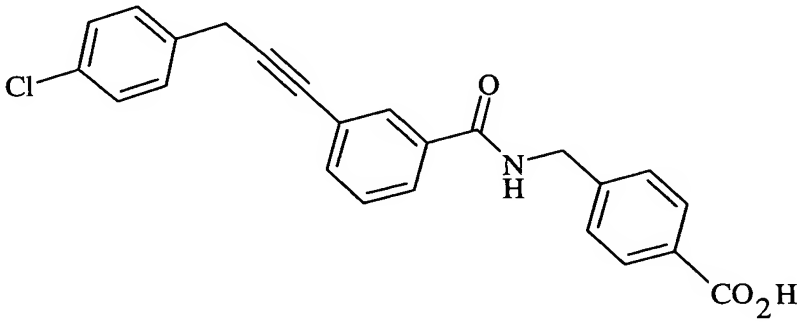
EXAMPLE 81

4-{[3-(3-Phenethylethynyl-benzoylamino]-methyl}-benzoic acid



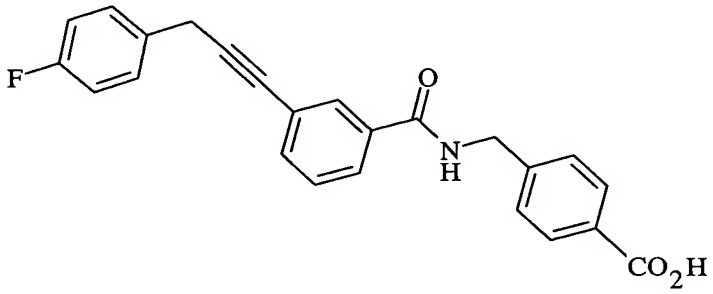
EXAMPLE 82

4-({3-[3-(4-Chloro-phenyl)-prop-1-ynyl]-benzoylamino}-methyl)-benzoic acid



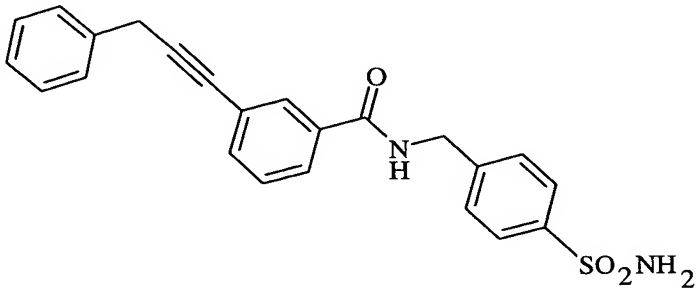
EXAMPLE 83

4-({3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-benzoylamino}-methyl)-benzoic acid



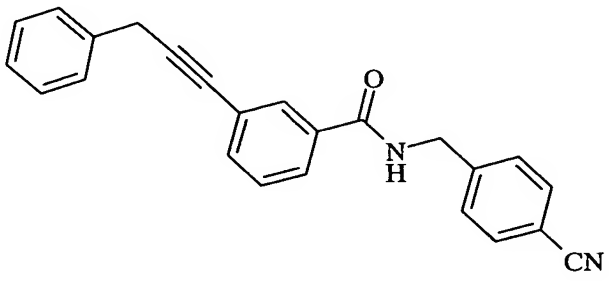
EXAMPLE 84

3-Phenylethynyl-*N*-(4-Sulfamoyl-benzyl)-benzamide



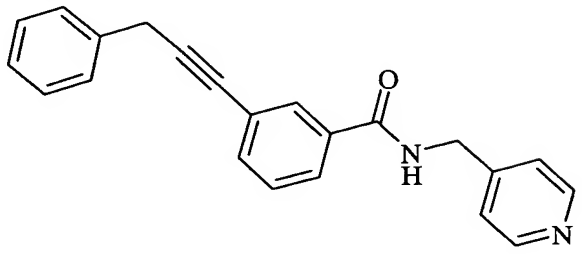
EXAMPLE 85

N-(4-Cyano-benzyl)-3-phenylethynyl-benzamide



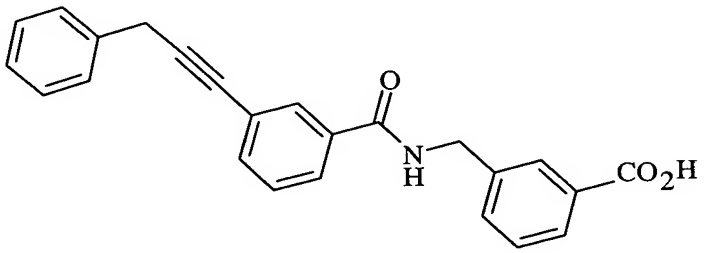
EXAMPLE 86

3-Phenethlethynyl-*N*-pyridin-4-yl-methyl-benzamide



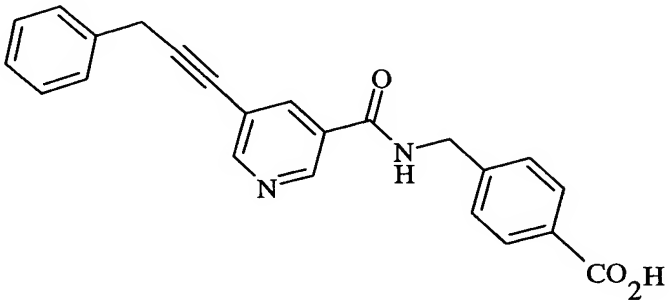
EXAMPLE 87

3-[{3-(3-Phenethylethynyl-benzoylamino)-methyl}-benzoic acid



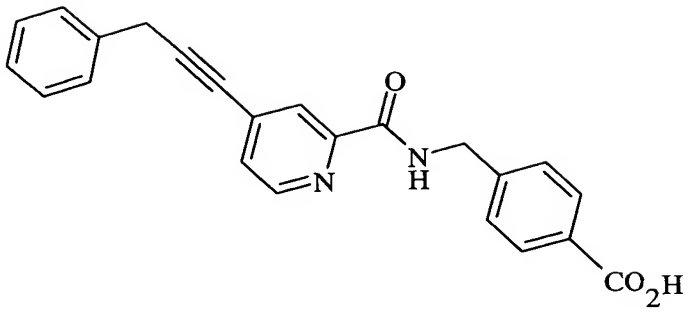
EXAMPLE 88

4-({[5-(3-Phenyl-prop-1-ynyl)-pyridine-3-carbonyl]-amino}-methyl)-benzoic acid



EXAMPLE 89

4-{[(Phenylethynyl-pyridine-2-carbonyl)-amino]-methyl}-benzoic acid



EXAMPLE 90

4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-2λ^4-benzo[1,2,6]thiadiazin-3-yl methyl]benzoic acid

EXAMPLE 91

4-[1-methyl-2,2,4-trioxo-6-(3-phenylprop-1-ynyl)-1,4-dihydro-2H-2λ^6-benzo[1,2,6]-thiadiazin-3-ylmethyl]benzoic acid

EXAMPLE 92

4-[1,1,3-Trioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid

EXAMPLE 93

2-(4-Methoxy-benzyl)-1,1-dioxo-7-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H, 1λ^6-benzo[1,2,4]thiadiazin-3-one

EXAMPLE 94

4-[1,1,3-Trioxo-7-(4-phenyl-but-1-ynyl)-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid

Representative Examples of other allosteric alkyne inhibitors of MMP-13 are named below:

3-(4-Methoxy-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;

N-(4-Methanesulfonyl-benzyl)-3-(4-methoxy-phenyl)-prop-1-ynyl)-benzamide;

3-(3-Methoxy-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-methoxy-phenyl)-prop-1-ynyl)-benzamide;
3-(4-Cyano-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(4-cyano-phenyl)-prop-1-ynyl)-benzamide;
3-(3-Cyano-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(3-cyano-phenyl)-prop-1-ynyl)-benzamide;
3-(4-Fluoro-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(4-fluoro-phenyl)-prop-1-ynyl)-benzamide;
3-(3-Fluoro-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(3-fluoro-phenyl)-prop-1-ynyl)-benzamide;
3-(4-Chloro-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(4-chloro-phenyl)-prop-1-ynyl)-benzamide;
3-(3-Chloro-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(3-chloro-phenyl)-prop-1-ynyl)-benzamide;
3-(4-Bromo-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(4-bromo-phenyl)-prop-1-ynyl)-benzamide;
3-(3-Bromo-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(3-bromo-phenyl)-prop-1-ynyl)-benzamide;
3-(4-Methanesulfanyl-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(4-methanesulfanyl-phenyl)-prop-1-ynyl)-benzamide;
3-(3-Methanesulfanyl-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(3-methanesulfanyl-phenyl)-prop-1-ynyl)-benzamide;
3-(4-Methyl-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(4-methyl-phenyl)-prop-1-ynyl)-benzamide;
3-(3-Methyl-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(3-methyl-phenyl)-prop-1-ynyl)-benzamide;
3-(3-Pyridin-4-yl-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(3-pyridin-4-yl-prop-1-ynyl)-benzamide;
3-(3-Pyridin-3-yl-prop-1-ynyl)-N-(4-carboxybenzyl)-benzamide;
N-(4-Methanesulfonyl-benzyl)-3-(3-pyridin-3-yl-prop-1-ynyl)-benzamide;

3-[3-(2-Methoxy-pyridin-4-yl)-prop-1-ynyl]-N-(4-carboxybenzyl)-benzamide; and

N-(4-Methanesulfonyl-benzyl)- 3-[3-(2-methoxy-pyridin-4-yl)-prop-1-ynyl]-benzamide.

Other allosteric alkyne inhibitors of MMP-13 include:

3-(4-Methoxy-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(4-methoxy-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(3-Methoxy-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-methoxy-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(4-Cyano-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(4-cyano-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(3-Cyano-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-cyano-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(4-Fluoro-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(4-fluoro-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(3-Fluoro-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-fluoro-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(4-Chloro-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(4-chloro-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(3-Chloro-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-chloro-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(4-Bromo-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(4-bromo-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(3-Bromo-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-bromo-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(4-Methanesulfanyl-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(4-methanesulfanyl-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(3-Methanesulfanyl-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-methanesulfanyl-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(4-Methyl-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(4-methyl-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(3-Methyl-phenyl)-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-methyl-phenyl)-prop-1-ynyl)-isonicotinamide;

3-(3-pyridin-4-yl-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-pyridin-4-yl-prop-1-ynyl)-isonicotinamide;

3-(3-Pyridin-3-yl-prop-1-ynyl)-N-(4-carboxybenzyl)-isonicotinamide;

N-(4-Methanesulfonyl-benzyl)-3-(3-pyridin-3-yl-prop-1-ynyl)-isonicotinamide;

3-[3-(2-Methoxy-pyridin-4-yl)-prop-1-ynyl]-N-(4-carboxybenzyl)-isonicotinamide; and

N-(4-Methanesulfonyl-benzyl)-3-[3-(2-methoxy-pyridin-4-yl)-prop-1-ynyl]-isonicotinamide.

Still other allosteric alkyne inhibitors of MMP-13 include:

2-Benzyl-4-methyl-1,1-dioxo-7-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one;

4-[4-Methyl-1,1,3-trioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid;

2-Benzyl-1,1-dioxo-7-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one;

4-[1,1,3-Trioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid;

2-Benzyl-4-methyl-1,1-dioxo-7-[3-(4-methoxyphenyl)-prop-1-ynyl]-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one;

2-Benzyl-1,1-dioxo-7-[3-(4-methoxyphenyl)-prop-1-ynyl]-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one;

4-{1,1,3-Trioxo-7-[3-(4-methoxyphenyl)-prop-1-ynyl]-4-methyl-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl}-benzoic acid;

4-{1,1,3-Trioxo-7-[3-(4-methoxyphenyl)-prop-1-ynyl]-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl}-benzoic acid;

2-Benzyl-4-methyl-1,1-dioxo-7-[3-(3-methoxyphenyl)-prop-1-ynyl]-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one;

2-Benzyl-1,1-dioxo-7-[3-(3-methoxyphenyl)-prop-1-ynyl]-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one;

4-{1,1,3-Trioxo-7-[3-(3-methoxyphenyl)-prop-1-ynyl]-4-methyl-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl}-benzoic acid; and

4-{1,1,3-Trioxo-7-[3-(3-methoxyphenyl)-prop-1-ynyl]-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl}-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

1-Methyl-6-(4-methoxy-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-1-methyl-6-(4-methoxy-phenyl)-prop-1-ynyl)-1H-quinolin-4-one;

1-Methyl-6-(3-methoxy-phenyl)-prop-1-ynyl)-3 -(4-carboxybenzyl)-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-1-methyl-6-(3-methoxy-phenyl)-prop-1-ynyl)-1H-quinolin-4-one;

6-(4-Cyano-phenyl)-prop-1-ynyl)-1-methyl-3-(4-carboxybenzyl)-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-cyano-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(3-Cyano-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

4-(4-Methanesulfonyl-benzyl)-6-(3-cyano-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(4-Fluoro-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-fluoro-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(3-Fluoro-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-fluoro-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(4-Chloro-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-chloro-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(3-Chloro-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-chloro-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(4-Bromo-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-bromo-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(3-Bromo-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-bromo-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(4-Methanesulfanyl-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-methanesulfanyl-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(3-Methanesulfanyl-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-methanesulfanyl-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(4-Methyl-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-methyl-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(3-Methyl-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-methyl-phenyl)-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(3-Pyridin-4-yl-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-pyridin-4-yl-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-(3-Pyridin-3-yl-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-pyridin-3-yl-prop-1-ynyl)-1-methyl-1H-quinolin-4-one;

6-[3-(2-Methoxy-pyridin-4-yl)-prop-1-ynyl]-3-(4-carboxybenzyl)-1-methyl-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-[3-(2-methoxy-pyridin-4-yl)-prop-1-ynyl]-1-methyl-1H-quinolin-4-one;

1-Methyl-6-(4-methoxy-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-1-methyl-6-(4-methoxy-phenyl)-prop-1-ynyl)-2,3-dihydro-1H-quinolin-4-one;

1-Methyl-6-(3-methoxy-phenyl)-prop-1-ynyl)-3 -(4-carboxybenzyl)-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-1-methyl-6-(3-methoxy-phenyl)-prop-1-ynyl)-2,3-dihydro-1H-quinolin-4-one;

6-(4-Cyano-phenyl)-prop-1-ynyl)-1-methyl-3-(4-carboxybenzyl)-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-cyano-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(3-Cyano-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

4-(4-Methanesulfonyl-benzyl)-6-(3-cyano-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(4-Fluoro-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-fluoro-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(3-Fluoro-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-fluoro-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(4-Chloro-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-chloro-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(3-Chloro-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-chloro-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(4-Bromo-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-bromo-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(3-Bromo-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-bromo-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(4-Methanesulfanyl-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-methanesulfanyl-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(3-Methanesulfanyl-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-methanesulfanyl-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(4-Methyl-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(4-methyl-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(3-Methyl-phenyl)-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-methyl-phenyl)-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(3-pyridin-4-yl-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-pyridin-4-yl-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-(3-Pyridin-3-yl-prop-1-ynyl)-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

3-(4-Methanesulfonyl-benzyl)-6-(3-pyridin-3-yl-prop-1-ynyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one;

6-[3-(2-Methoxy-pyridin-4-yl)-prop-1-ynyl]-3-(4-carboxybenzyl)-1-methyl-2,3-dihydro-1H-quinolin-4-one; and

3-(4-Methanesulfonyl-benzyl)-6-[3-(2-methoxy-pyridin-4-yl)-prop-1-ynyl]-1-methyl-2,3-dihydro-1H-quinolin-4-one.

Still other allosteric alkyne inhibitors of MMP-13 include:

2-(Phenyl)-prop-1-ynyl)-6-benzyl-4H-thiazolo[3,2-a]pyridin-5-one;

2-(4-Methoxy-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(4-methoxy-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(3-Methoxy-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(3-methoxy-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(4-Cyano-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(4-cyano-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(3-Cyano-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(3-cyano-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(4-Fluoro-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(4-fluoro-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(3-Fluoro-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(3-fluoro-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(4-Chloro-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(4-chloro-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(3-Chloro-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(3-chloro-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(4-Bromo-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(4-bromo-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(3-Bromo-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(3-bromo-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(4-Methanesulfanyl-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(4-methanesulfanyl-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(3-Methanesulfanyl-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(3-methanesulfanyl-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(4-Methyl-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(4-methyl-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(3-Methyl-phenyl)-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(3-methyl-phenyl)-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(3-Pyridin-4-yl-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(3-pyridin-4-yl-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-(3-Pyridin-3-yl-prop-1-ynyl)-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one;

6-(4-Methanesulfonyl-benzyl)-2-(3-pyridin-3-yl-prop-1-ynyl)-4H-thiazolo[3,2-a]pyridin-5-one;

2-[3-(2-Methoxy-pyridin-4-yl)-prop-1-ynyl]-6-(4-carboxybenzyl)-4H-thiazolo[3,2-a]pyridin-5-one; and

6-(4-Methanesulfonyl-benzyl)-2-[3-(2-methoxy-pyridin-4-yl)-prop-1-ynyl]-4H-thiazolo[3,2-a]pyridin-5-one.

Still other allosteric alkyne inhibitors of MMP-13 include:

2-(Phenyl-prop-1-ynyl)-5-(4-benzyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Methoxy-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-methoxy-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Methoxy-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-methoxy-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Cyano-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-cyano-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Cyano-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-cyano-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Fluoro-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-fluoro-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Fluoro-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-fluoro-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Chloro-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-chloro-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Chloro-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-chloro-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Bromo-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-bromo-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Bromo-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-bromo-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Methanesulfanyl-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-methanesulfanyl-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Methanesulfanyl-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-methanesulfanyl-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Methyl-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-methyl-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Methyl-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-methyl-phenyl)-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Pyridin-4-yl-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-pyridin-4-yl-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Pyridin-3-yl-prop-1-ynyl)-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-pyridin-3-yl-prop-1-ynyl)-5H-thieno[3,2-c]pyridin-4-one;

2-[3-(2-Methoxy-pyridin-4-yl)-prop-1-ynyl]-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-[3-(2-methoxy-pyridin-4-yl)-prop-1-ynyl]-5H-thieno[3,2-c]pyridin-4-one;

2-(Phenyl-prop-1-ynyl)-5-(4-benzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Methoxy-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-methoxy-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Methoxy-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-methoxy-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Cyano-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-cyano-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Cyano-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-cyano-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Fluoro-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-fluoro-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Fluoro-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-fluoro-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Chloro-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-chloro-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Chloro-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-chloro-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Bromo-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-bromo-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Bromo-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-bromo-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Methanesulfanyl-phenyl)-prop-1-ynyl)-7-methyl-5-(4-carboxybenzyl)-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-methanesulfanyl-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Methanesulfanyl-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-methanesulfanyl-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(4-Methyl-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(4-methyl-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Methyl-phenyl)-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-methyl-phenyl)-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Pyridin-4-yl-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-pyridin-4-yl-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-(3-Pyridin-3-yl-prop-1-ynyl)-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

5-(4-Methanesulfonyl-benzyl)-2-(3-pyridin-3-yl-prop-1-ynyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one;

2-[3-(2-Methoxy-pyridin-4-yl)-prop-1-ynyl]-5-(4-carboxybenzyl)-7-methyl-5H-thieno[3,2-c]pyridin-4-one; and

5-(4-Methanesulfonyl-benzyl)-2-[3-(2-methoxy-pyridin-4-yl)-prop-1-ynyl]-7-methyl-5H-thieno[3,2-c]pyridin-4-one.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-2λ^4-benzo[d][1,2]thiazin-3-ylmethyl]-benzoic acid; and

4-[2,2,4-trioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-2λ^6-benzo[d][1,2]thiazin-3-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[1,3-dioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1*H*-3λ^4-thia-2,6-diaza-naphthalen-2-ylmethyl]-benzoic acid; and

4-[1,3,3-trioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1*H*-3λ^6-thia-2,6-diaza-naphthalen-2-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-4*H*-2λ^4-benzo[e][1,2,3]oxathiazin-3-ylmethyl]-benzoic acid; and

4-[2,2,4-trioxo-6-(3-phenyl-prop-1-ynyl)-4*H*-2λ^6-benzo[e][1,2,3]oxathiazin-3-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-4*H*-1-oxa-2λ^4-thia-3,7-diaza-naphthalen-3-ylmethyl]-benzoic acid; and

4-[2,2,4-trioxo-6-(3-phenyl-prop-1-ynyl)-4*H*-1-oxa-2λ^6-thia-3,7-diaza-naphthalen-3-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-2λ^4-benzo[1,2,6]thiadiazin-3-ylmethyl]-benzoic acid;

4-[2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-2l^4-benzo[1,2,6]thiadiazin-3-ylmethyl]-benzoic acid; and

4-[1-methyl-2,2,4-trioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-2l^6-benzo[1,2,6]thiadiazin-3-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

3-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-2l^4-pyrido[3,4-c][1,2,6]thiadiazin--3-ylmethyl]-benzoic acid;

3-[2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-2l^4-pyrido[3,4-c][1,2,6]thiadiazin--3-ylmethyl]-benzoic acid; and

3-[1-methyl-2,2,4-trioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-2l^6-pyrido[3,4-c][1,2,6]thiadiazin--3-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[1-oxo-7-(3-phenyl-prop-1-ynyl)-1*H*-1l^4-benzo[e][1,2]thiazin-2-ylmethyl]-benzoic acid; and

4-[1,1-dioxo-7-(3-phenyl-prop-1-ynyl)-1*H*-1l^6-benzo[e][1,2]thiazin-2-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[1-oxo-7-(3-phenyl-prop-1-ynyl)-1*H*-1l^4- thia-2,6-diaza-naphthalen-2-ylmethyl]-benzoic acid; and

4-[1,1-dioxo-7-(3-phenyl-prop-1-ynyl)-1*H*-1l^6- thia-2,6-diaza-naphthalen-2-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[4-methyl-1,3-dioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1*H*-1l^4-thia-2,4,6-triaza-naphthalen-2-ylmethyl]-benzoic acid;

4-[1,3-dioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1*H*-1l^4-thia-2,4,6-triaza-naphthalen-2-ylmethyl]-benzoic acid; and

4-[4-methyl-1,1,3-trioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1*H*-1λ^6-thia-2,4,6-triaza-naphthalen-2-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[4-methyl-1,3-dioxo-6-(3-phenyl-prop-1-ynyl)3,4-dihydro-1*H*-1λ^4-thieno[2,3-e][1,2,4]thiadiazin-2-ylmethyl]-benzoic acid;

4-[1,3-dioxo-6-(3-phenyl-prop-1-ynyl)3,4-dihydro-1*H*-1λ^4-thieno[2,3-e][1,2,4]thiadiazin-2-ylmethyl]-benzoic acid;

4-[4-methyl-1,1,3-trioxo-6-(3-phenyl-prop-1-ynyl)3,4-dihydro-1*H*-1λ^6-thieno[2,3-e][1,2,4]thiadiazin-2-ylmethyl]-benzoic acid;

4-[1,1,3-trioxo-6-(3-phenyl-prop-1-ynyl)3,4-dihydro-1*H*-1λ^6-thieno[2,3-e][1,2,4]thiadiazin-2-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[1-oxo-6-(3-phenyl-prop-1-ynyl)-1*H*-1λ^4-thieno[2,3-e][1,2]thiazin-2-ylmethyl]-benzoic acid; and

4-[1,1-dioxo-6-(3-phenyl-prop-1-ynyl)-1*H*-1λ^6-thieno[2,3-e][1,2]thiazin-2-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[1,3-dioxo-6-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1*H*-1λ^4-thieno[2,3-e][1,2]thiazin-2-ylmethyl]-benzoic acid; and

4-[1,1,3-trioxo-6-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1*H*-1λ^6-thieno[2,3-e][1,2]thiazin-2-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[4,6-dioxo-2-(3-phenyl-prop-1-ynyl)-6,7-dihydro-4*H*-thieno[3,2-c]pyridin-5-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[4-oxo-2-(3-phenyl-prop-1-ynyl)-4*H*-thieno[3,2-c]pyridin-5-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[4-oxo-2-(3-phenyl-prop-1-ynyl)-4*H*-1,4λ^4-dithia-3,5-diaza-inden-5-ylmethyl]-benzoic acid; and

4-[4,4-dioxo-2-(3-phenyl-prop-1-ynyl)-4*H*-1,4λ^6-dithia-3,5-diaza-inden-5-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[4,6-dioxo-2-(3-phenyl-prop-1-ynyl)-6,7-dihydro-4*H*-1,4λ^4-dithia-3,5-diaza-inden-5-ylmethyl]-benzoic acid; and

4-[4,4,6-trioxo-2-(3-phenyl-prop-1-ynyl)-6,7-dihydro-4*H*-1,4λ^6-dithia-3,5-diaza-inden-5-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[4,6-dioxo-2-(3-phenyl-prop-1-ynyl)-6,7-dihydro-4*H*-thiazolo[4,5-c]pyridin-5-ylmethyl-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[7-methyl-4,6-dioxo-2-(3-phenyl-prop-1-ynyl)-6,7-dihydro-h*H*-1,4λ^4-dithia-3,5,7-triaza-inden-5-ylmethyl]-benzoic acid;

4-[4,6-dioxo-2-(3-phenyl-prop-1-ynyl)-6,7-dihydro-h*H*-1,4λ^4-dithia-3,5,7-triaza-inden-5-ylmethyl]-benzoic acid;

4-[7-methyl-4,4,6-trioxo-2-(3-phenyl-prop-1-ynyl)-6,7-dihydro-h*H*-1,4λ^6-dithia-3,5,7-triaza-inden-5-ylmethyl]-benzoic acid; and

4-[4,4,6-trioxo-2-(3-phenyl-prop-1-ynyl)-6,7-dihydro-h*H*-1,4λ^6-dithia-3,5,7-triaza-inden-5-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[4-oxo-2-(3-phenyl-prop-1-ynyl)-4*H*-thiazolo[4,5-c]pyridin-5-ylmethyl]-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

N-(4-Cyano-benzyl)-3-(3-[1,2,3]-triazol-1-yl-prop-1-ynyl)-benzamide;

N-(4-Cyano-benzyl)-3-(3-[1,2,3]-triazol-1-yl-prop-1-ynyl)-benzamide;

4-({3-[3-(4-Chloro-phenyl)-prop-1-ynyl]-benzoylamino}-methyl)-benzoic acid;

4-({3-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-benzoylamino}-methyl)-benzoic acid;

3-Phenylethynyl-N-(4-Sulfamoyl-benzyl)-benzamide;

N-(4-Cyano-benzyl)-3-phenylethynyl-benzamide;

3-Phenethylethynyl-N-pyridin-4-yl-methyl-benzamide; and

3-[[3-(3-Phenethylethynyl-benzoylamino]-methyl}-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-({[5-(3-Phenyl-prop-1-ynyl)-pyridine-3-carbonyl]-amino}-methyl)-benzoic acid; and

4-{[(Phenylethynyl-pyridine-2-carbonyl)-amino]-methyl}-benzoic acid.

Still other allosteric alkyne inhibitors of MMP-13 include:

4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-2λ^4-benzo[1,2,6]thiadiazin-3-yl methyl]benzoic acid;

4-[1-methyl-2,2,4-trioxo-6-(3-phenylprop-1-ynyl)-1,4-dihydro-2H-2λ^6-benzo[1,2,6]thiadiazin-3-ylmethyl]benzoic acid;

4-[1,1,3-Trioxo-7-(3-phenyl-prop-1-ynyl)-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid;

2-(4-Methoxy-benzyl)-1,1-dioxo-7-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-1λ^6-benzo[1,2,4]thiadiazin-3-one; and

4-[1,1,3-Trioxo-7-(4-phenyl-but-1-ynyl)-3,4-dihydro-1H-1λ^6-benzo[1,2,4]thiadiazin-2-ylmethyl]-benzoic acid.

The allosteric inhibitors of MMP-13 have been evaluated in standard assays to determine inhibitor activity with various MMP enzymes, as mentioned above. The assays measure the amount by which a test compound reduces the hydrolysis of a thiopeptolide substrate catalyzed by a matrix metalloproteinase enzyme. Such assays are described in detail by Ye et al., in *Biochemistry*, 1992;31(45):11231-11235, which is incorporated herein by reference. One such assay is described below in Biological Method 1.

Some of the particular methods described below use the catalytic domain of the MMP-13 enzyme, namely matrix metalloproteinase-13 catalytic domain ("MMP-13CD"), rather than the corresponding full-length enzyme, MMP-13. It has been shown previously by Ye Qi-Zhuang, Hupe D., and Johnson L. (*Current Medicinal Chemistry*, 1996;3:407-418) that inhibitor activity against a catalytic

domain of an MMP is predictive of the inhibitor activity against the respective full-length MMP enzyme.

Thiopeptolide substrates show virtually no decomposition or hydrolysis at or below neutral pH in the absence of a matrix metalloproteinase enzyme. A typical thiopeptolide substrate commonly utilized for assays is Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt. A 100 μL assay mixture will contain 50 mM of N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid buffer ("HEPES," pH 7.0), 10 mM $CaCl_2$, 100 μM thiopeptolide substrate, and 1 mM 5,5'-dithio-bis-(2-nitro-benzoic acid) (DTNB). The thiopeptolide substrate concentration may be varied, for example from 10 to 800 μM to obtain K_m and K_{cat} values. The change in absorbance at 405 nm is monitored on a Thermo Max microplate reader (molecular Devices, Menlo Park, CA) at room temperature (22°C). The calculation of the amount of hydrolysis of the thiopeptolide substrate is based on $E_{412} = 13600\ M^{-1}\ cm^{-1}$ for the DTNB-derived product 3-carboxy-4-nitrothiophenoxide. Assays are carried out with and without matrix metalloproteinase inhibitor compounds, and the amount of hydrolysis is compared for a determination of inhibitory activity of the test compounds.

Test compounds were evaluated at various concentrations in order to determine their respective IC_{50} values, the micromolar concentration of compound required to cause a 50% inhibition of catalytic activity of the respective enzyme.

It should be appreciated that the assay buffer used with MMP-3CD was 50 mM N-morpholinoethane sulfonate ("MES") at pH 6.0 rather than the HEPES buffer at pH 7.0 described above.

It should be appreciated that allosteric inhibitors of MMP-13 may be readily identified by assaying a test compound for inhibition of MMP-13 according to Biological Methods 1 or 2, and further assaying the test compound for allosteric inhibition of MMP-13 according to Biological Methods 3 or 4, as described below.

BIOLOGICAL METHOD 1

Thiopeptolide substrates show virtually no decomposition or hydrolysis at or below neutral pH in the absence of a matrix metalloproteinase enzyme. A typical thiopeptolide substrate commonly utilized for assays is Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt. A 100 μL assay mixture will contain 50 mM of N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid buffer ("HEPES," pH 7.0), 10 mM $CaCl_2$, 100 μM thiopeptolide substrate, and 1 mM 5,5'-dithio-bis-(2-nitro-benzoic acid) (DTNB). The thiopeptolide substrate concentration may be varied, for example from 10 to 800 μM to obtain K_m and K_{cat} values. The change in absorbance at 405 nm is monitored on a Thermo Max microplate reader (molecular Devices, Menlo Park, CA) at room temperature (22°C). The calculation of the amount of hydrolysis of the thiopeptolide substrate is based on $E_{412} = 13600\ M^{-1}\ cm^{-1}$ for the DTNB-derived product 3-carboxy-4-nitrothiophenoxide. Assays are carried out with and without matrix metalloproteinase inhibitor compounds, and the amount of hydrolysis is compared for a determination of inhibitory activity of the test compounds.

Test compounds were evaluated at various concentrations in order to determine their respective IC_{50} values, the micromolar concentration of compound required to cause a 50% inhibition of catalytic activity of the respective enzyme.

It should be appreciated that the assay buffer used with MMP-3CD was 50 mM N-morpholinoethane sulfonate ("MES") at pH 6.0 rather than the HEPES buffer at pH 7.0 described above.

The test described above for the inhibition of MMP-13 was also adapted and used to determine the ability of the compounds of formula (A) to inhibit the matrix metalloproteases MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14. The results obtained show that the allosteric inhibitors of MMP-13 generally have IC_{50} values for MMP-13 which are about 100 times lower than the IC_{50} values for the same allosteric inhibitors of MMP-13 with respect to the other matrix metalloproteases tested.

BIOLOGICAL METHOD 2

Allosteric inhibitors of MMP-13 have been evaluated for their ability to inhibit MMP-13. Inhibitor activity of allosteric inhibitors of MMP-13 versus other MMPs may be determined using, for example, MMP-1FL, which refers to full length interstitial collagenase; MMP-2FL, which refers to full length Gelatinase A; MMP-3CD, which refers to the catalytic domain of stromelysin; MMP-7FL, which refers to full length matrilysin; MMP-9FL, which refers to full length Gelatinase B; MMP-13CD, which refers to the catalytic domain of collagenase 3; and MMP-14CD, which refers to the catalytic domain of MMP-14. Test compounds can be evaluated at various concentrations in order to determine their respective IC_{50} values, the micromolar concentration of compound required to cause a 50% inhibition of the hydrolytic activity of the respective enzyme.

The results of the above assays with other MMPs have established that the allosteric inhibitors of MMP-13 are potent and selective inhibitors of MMP-13 enzymes. Because of this potent and selective inhibitory activity, the allosteric inhibitors of MMP-13 are especially useful, in combination with a selective inhibitor of COX-2 that is not celecoxib or valdecoxib.

BIOLOGICAL METHOD 3

Fluorigenic peptide-1 substrate based assay for identifying allosteric inhibitors of MMP-13CD:

Final assay conditions:

50 mM HEPES buffer (pH 7.0)

10 mM $CaCl_2$

10 μM fluorigenic peptide-1 ("FP1") substrate

0 or 15 mM acetohydroxamic acid (AcNHOH) = 1 K_d

2% DMSO (with or without inhibitor test compound)

0.5 nM MMP-13CD enzyme

Stock solutions:

1) 10X assay buffer: 500 mM HEPES buffer (pH 7.0) plus 100 mM $CaCl_2$

2) 10 mM FP1 substrate: (Mca)-Pro-Leu-Gly-Leu-(Dnp)-Dpa-Ala-Arg-NH_2 (Bachem, M-1895; "A novel coumarin-labeled peptide for sensitive continuous assays of the matrix metalloproteinases," Knight C.G., Willenbrock F., and Murphy, G., *FEBS Lett.*, 1992;296:263-266). Prepared 10 mM stock by dissolving 5 mg FP1 in 0.457 mL DMSO.

3) 3 M AcNHOH: Prepared by adding 4 mL H_2O and 1 mL 10X assay buffer to 2.25 g AcNHOH (Aldrich 15,903-4). Adjusted pH to 7.0 with NaOH. Diluted volume to 10 mL with H_2O. Final solution contained 3 M AcNHOH, 50 mM HEPES buffer (pH 7.0), and 10 mM $CaCl_2$.

4) AcNHOH dilution buffer: 50 mM HEPES buffer (pH 7.0) plus 10 mM $CaCl_2$

5) MMP-13CD enzyme: Stock concentration = 250 nM.

6) Enzyme dilution buffer: 50 mM HEPES buffer (pH 7.0), 10 mM $CaCl_2$, and 0.005% BRIJ 35 detergent (Calbiochem 203728; Protein Grade, 10%)

Procedure (for one 96-well microplate):

A. *Prepared assay mixture:*

1100 µL 10X assay buffer

11 µL 10 mM FP1

55 µL 3 M AcNHOH or 55 µL AcNHOH dilution buffer

8500 µL H_2O

B. *Diluted MMP-13CD to 5 nM working stock:*

22 µL MMP-13CD (250 nM)

1078 µL enzyme dilution buffer

C. *Ran kinetic assay:*

1. Dispensed 2 µL inhibitor test sample (in 100% DMSO) into well.
2. Added 88 µL assay mixture and mixed well, avoiding bubbles.
3. Initiated reactions with 10 µL of 5 nM MMP-13CD; mixed well, avoiding bubbles.
4. Immediately measured the kinetics of the reactions at room temperature.

Fluorimeter: F_{max} Fluorescence Microplate Reader & SOFTMAX PRO Version 1.1 software (Molecular Devices Corporation; Sunnyvale, CA 94089).

Protocol menu:

excitation: 320 nm	emission: 405 nm
run time: 15 min	interval: 29 sec
RFU min: -10	RFU max: 200
V_{max} points: 32/32	

D. Compared % of control activity and/or IC_{50} with inhibitor test compound ±AcNHOH.

Hydrolysis of the fluorigenic peptide-1 substrate, [(Mca)Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2; Bachem, catalog number M-1895], wherein "Mca" is (7-methoxy-coumarin-4-yl)acetyl and "Dpa" is (3-[2,4-dinitrophenyl]-L-2,3-diaminopropionyl), was used to screen for MMP-13 catalytic domain (CD) inhibitors. (Dpa may also be abbreviated as "Dnp".) Reactions (100 µL) contained 0.05 M Hepes buffer (pH 7), 0.01 M calcium chloride, 0.005% polyoxyethylene (23) lauryl ether ("Brij 35"), 0 or 15 mM acetohydroxamic acid, 10 µM FP1, and 0.1 mM to 0.5 nM inhibitor in DMSO (2% final).

After recombinant human MMP-13CD (0.5 nM final) was added to initiate the reaction, the initial velocity of FP1 hydrolysis was determined by monitoring the increase in fluorescence at 405 nm (upon excitation at 320 nm) continuously for up to 30 minutes on a microplate reader at room temperature. Alternatively, an endpoint read can also be used to determine reaction velocity provided the initial fluorescence of the solution, as recorded before addition of enzyme, is subtracted from the final fluorescence of the reaction mixture. The inhibitor was assayed at different concentration values, such as, for example, 100 µM, 10 µM, 1 µM, 100 nM, 10 nM, and 1 nM. Then the inhibitor concentration was plotted on the X-axis against the percentage of control activity observed for inhibited experiments versus uninhibited experiments (i.e., (velocity with inhibitor) divided by (velocity without inhibitor) × 100) on the Y-axis to determine IC_{50} values. This determination was done for experiments done in the presence, and

experiments done in the absence, of acetohydroxamic acid. Data were fit to the equation: percent control activity = $100/[1+(([I]/IC_{50})^{slope})]$, where [I] is the inhibitor concentration, IC_{50} is the concentration of inhibitor where the reaction rate is 50% inhibited relative to the control, and slope is the slope of the IC_{50} curve at the curve's inflection point, using nonlinear least-squares curve-fitting equation regression.

Results may be expressed as an IC_{50} Ratio (+/-) ratio, which means a ratio of the IC_{50} of the inhibitor with MMP-13 and a inhibitor to the catalytic zinc of MMP-13, divided by the IC_{50} of the inhibitor with MMP-13 without the inhibitor to the catalytic zinc of MMP-13. Allosteric inhibitors of MMP-13 have an IC_{50} Ratio (+/-) ratio of less than 1, and are synergistic with the inhibitor to the catalytic zinc of MMP-13 such as, for example, AcNHOH. Compounds which are not allosteric inhibitors of MMP-13 will be inactive in the assay or will have an IC_{50} Ratio (+/-) of greater than 1, unless otherwise indicated. Results can be confirmed by kinetics experiments which are well known in the biochemical art.

BIOLOGICAL METHOD 4

Fluorigenic peptide-1 based assay for identifying allosteric inhibitors of matrix metalloproteinase-13 catalytic domain ("MMP-13CD"):

In a manner similar to Biological Method 3, an assay is run wherein 1,10-phenanthroline is substituted for acetohydroxamic acid to identify allosteric inhibitors of MMP-13CD.

Animal models may be used to establish that the instant allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, or an N-oxide thereof, would be useful for preventing, treating, and inhibiting cartilage damage, and thus for treating osteoarthritis, for example.

The newly discovered ability of an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, to inhibit cartilage damage, alleviate pain, and treat osteoarthritis may be established in animal models as described below.

BIOLOGICAL METHOD 5

Selective inhibitors of COX-2 may be identified by screening a test compound in the following assays.

Human In vitro assays

Human cell-based COX-1 assay:

Human peripheral blood obtained from healthy volunteers can be diluted to 1/10 volume with 3.8% sodium citrate solution. The platelet-rich plasma immediately obtained can be washed with 0.14 M sodium chloride containing 12 mM Tris-HCl (pH 7.4) and 1.2 mM EDTA. Platelets can then be washed with platelet buffer (Hanks buffer (Ca free) containing 0.2% BSA and 20 mM Hepes). Finally, the human washed platelets (HWP) can be suspended in platelet buffer at the concentration of 2.85×10^8 cells/ml and stored at room temperature until use. The HWP suspension (70 μl aliquots, final 2.0×10^7 cells/ml) can be placed in a 96-well U bottom plate and 10 μl aliquots of 12.6 mM calcium chloride added. Platelets can be incubated with A23187 (final 10 μM, Sigma) with test compound (0.1 - 100 μM) dissolved in DMSO (final concentration; less than 0.01%) at 37°C for 15 minutes. The reaction can be stopped by addition of EDTA (final 7.7 mM) and TxB2 in the supernatant quantitated by using a radioimmunoassay kit (Amersham) according to the manufacturer's procedure.

Human cell-based COX-2 assay:

The human cell based COX-2 assay can be carried out as previously described (Moore et al., Inflamm. Res., 45, 54, 1996). Confluent human umbilical vein endothelial cells (HUVECs, Morinaga) in a 96-well flat bottom plate can be washed with 80 ml of RPMI1640 containing 2% FBS and incubated with hIL-1β (final concentration 300 U/ml, R & D Systems) at 37°C for 24 hours. After washing, the activated HUVECs can be incubated with test compound (final concentration; 0.1nM-1μM) dissolved in DMSO (final concentration; less than 0.01%) at 37°C for 20 minutes and stimulated with A23187 (final concentration 30 mM) in Hanks buffer containing 0.2% BSA, 20 mM Hepes at 37°C for 15 minutes. 6-Keto-$PGF_{1\alpha}$, stable metabolite of PGI2, in the supernatant can be quantitated by using a radioimmunoassay method (antibody; Preseptive Diagnostics, SPA; Amersham).

Canine In vitro assays:

The following canine cell based COX 1 and COX-2 assays have been reported in Ricketts et al., *Evaluation of Selective Inhibition of Canine Cyclooxygenase 1 and 2 by Carprofen and Other Nonsteroidal Anti-inflammatory Drugs,* American Journal of Veterinary Research, 59 (11), 1441-1446.

Protocol for Evaluation of Canine COX-1 Activity:

Test compounds can be solubilized and diluted the day before the assay can be to be conducted with 0.1 mL of DMSO/9.9 mL of Hank's balanced salts solution (HBSS) and stored overnight at 4°C. On the day that the assay can be carried out, citrated blood can be drawn from a donor dog, centrifuged at 190 x g for 25 minutes at room temperature and the resulting platelet-rich plasma can then be transferred to a new tube for further procedures. The platelets can be washed by centrifuging at 1500 x g for 10 minutes at room temperature. The platelets can be washed with platelet buffer comprising Hank's buffer (Ca free) with 0.2% bovine serum albumin (BSA) and 20 mM HEPES. The platelet samples can then be adjusted to 1.5 x 10^7/mL, after which 50 µl of calcium ionophore (A23187) together with a calcium chloride solution can be added to 50 µl of test compound dilution in plates to produce final concentrations of 1.7 µM A23187 and 1.26 mM Ca. Then, 100 µl of canine washed platelets can be added and the samples can be incubated at 37°C for 15 minutes, after which the reaction can be stopped by adding 20 µl of 77 mM EDTA. The plates can then be centrifuged at 2000 x g for 10 minutes at 4°C, after which 50 µl of supernatant can be assayed for thromboxane B_2 (TXB_2) by enzyme-immunoassay (EIA). The pg/mL of TXB_2 can be calculated from the standard line included on each plate, from which it can be possible to calculate the percent inhibition of COX-1 and the IC_{50} values for the test compounds.

Protocol for Evaluation of Canine COX-2 Activity:

A canine histocytoma (macrophage-like) cell line from the American Type Culture Collection designated as DH82, can be used in setting up the protocol for evaluating the COX-2 inhibition activity of various test compounds. There can be added to flasks of these cells 10 µg/mL of LPS, after which the flask cultures can be incubated overnight. The same test compound dilutions as described above for

the COX-1 protocol can be used for the COX-2 assay and can be prepared the day before the assay can be carried out. The cells can be harvested from the culture flasks by scraping and can then be washed with minimal Eagle's media (MEM) combined with 1% fetal bovine serum, centrifuged at 1500 rpm for 2 minutes and adjusted to a concentration of 3.2×10^5 cells/mL. To 50 µl of test compound dilution there can be added 50 µl of arachidonic acid in MEM to give a 10 µM final concentration and there can be added as well 100 µl of cell suspension to give a final concentration of 1.6×10^5 cells/mL. The test sample suspensions can be incubated for 1 hour and then centrifuged at 1000 rpm for 10 minutes at 4° C, after which 50 µl aliquots of each test compound sample can be delivered to EIA plates. The EIA can be performed for prostaglandin E_2 (PGE_2) and the pg/mL concentration of PGE_2 can be calculated from the standard line included on each plate. From this data it can be possible to calculate the percent inhibition of COX-2 and the IC_{50} values for the test compounds. Repeated investigations of COX-1 and COX-2 inhibition can be conducted over the course of several months. The results are averaged and a single COX-1:COX-2 ratio is calculated.

Whole blood assays for COX-1 and COX-2 are known in the art such as the methods described in C. Brideau, et al., *A Human Whole Blood Assay for Clinical Evaluation of Biochemical Efficacy of Cyclooxygenase Inhibitors*, Inflammation Research, Vol. 45, pp. 68-74 (1996). These methods may be applied with feline, canine or human blood as needed.

BIOLOGICAL METHOD 6

Carrageenan induced foot edema in rats

Male Sprague-Dawley rats (5 weeks old, Charles River Japan) can be fasted overnight. A line can be drawn using a marker above the ankle on the right hind paw and the paw volume (V0) can be measured by water displacement using a plethysmometer (Muromachi). Animals can be given orally either vehicle (0.1% methyl cellulose or 5% Tween 80) or a test compound (2.5 ml per 100g body weight). One hour later, the animals can then be injected intradermally with □-

carrageenan (0.1 ml of 1% w/v suspension in saline, Zushikagaku) into right hind paw (Winter et al., Proc. Soc. Exp. Biol. Med., 111, 544, 1962; Lombardino et al., Arzneim. Forsch., 25, 1629, 1975) and three hours later, the paw volume (V3) can be measured and the increase in volume (V3-V0) calculated. Since maximum inhibition attainable with classical NSAIDs is 60-70%, ED_{30} values can be calculated.

BIOLOGICAL METHOD 7

Gastric ulceration in rats:

The gastric ulcerogenicity of test compound can be assessed by a modification of the conventional method (Ezer et al., J. Pharm. Pharmacol., 28, 655, 1976; Cashin et al., J. Pharm. Pharmacol., 29, 330 - 336, 1977). Male Sprague-Dawley rats (5 weeks old, Charles River Japan), fasted overnight, can be given orally either vehicle (0.1% methyl cellulose or 5% Tween 80) or a test compound (1 ml per 100g body weight). Six hours after, the animals can be sacrificed by cervical dislocation. The stomachs can be removed and inflated with 1% formalin solution (10 ml). Stomachs can be opened by cutting along the greater curvature. From the number of rats that showed at least one gastric ulcer or haemorrhaging erosion (including ecchymosis), the incidence of ulceration can be calculated. Animals did not have access to either food or water during the experiment.

BIOLOGICAL METHOD 8

Canine whole blood ex vivo determinations of COX-1 and COX-2 activity inhibition

The in vivo inhibitory potency of a test compound against COX-1 and COX-2 activity may be evaluated using an ex vivo procedure on canine whole blood. Three dogs can be dosed with 5 mg/kg of the test compound administered by oral gavage in 0.5% methylcellulose vehicle and three dogs can be untreated. A zero-hour blood sample can be collected from all dogs in the study prior to dosing, followed by 2- and 8-hour post-dose blood sample collections. Test tubes can be prepared containing 2μL of either (A) calcium ionophore A23187 giving a 50 μM

final concentration, which stimulates the production of thromboxane B_2 (TXB_2) for COX-1 activity determination; or of (B) lipopolysaccharide (LPS) to give a 10 μg/mL final concentration, which stimulates the production of prostaglandin E_2 (PGE_2) for COX-2 activity determination. Test tubes with unstimulated vehicle can be used as controls. A 500 μL sample of blood can be added to each of the above-described test tubes, after which they can be incubated at 37°C for one hour in the case of the calcium ionophore-containing test tubes and overnight in the case of the LPS-containing test tubes. After incubation, 10 μL of EDTA can be added to give a final concentration of 0.3%, in order to prevent coagulation of the plasma which sometimes occurs after thawing frozen plasma samples. The incubated samples can be centrifuged at 4°C and the resulting plasma sample of ~200 μL can be collected and stored at –20°C in polypropylene 96-well plates. In order to determine endpoints for this study, enzyme immunoassay (EIA) kits available from Cayman can be used to measure production of TXB_2 and PGE_2, utilizing the principle of competitive binding of tracer to antibody and endpoint determination by colorimetry. Plasma samples can be diluted to approximate the range of standard amounts which would be supplied in a diagnostic or research tools kit, i.e., 1/500 for TXB_2 and 1/750 for PGE_2 .

COX inhibition is observed when the measured percent inhibition is greater than that measured for untreated controls. The percent inhibition in the above table is calculated in a straightforward manner in accordance with the following equation:

$$\% \text{ Inhibition (2-hour)} = \frac{(PGE_2 \text{ at } t = 0) - (PGE_2 \text{ at } t = 2)}{(PGE_2 \text{ at } t = 0)}$$

Data Analysis:

Statistical program packages, SYSTAT (SYSTAT, INC.) and StatView (Abacus Cencepts, Inc.) for Macintosh can be used. Differences between test compound treated group and control group can be tested for using ANOVA. The IC_{50} (ED30) values can be calculated from the equation for the log-linear regression line of concentration (dose) versus percent inhibition.

The selective COX-2 inhibitors described above have been, or could have been, identified by at least one of the methods described above and show, or would show, IC_{50} values of 0.001 μM to 3 μM with respect to inhibition of COX-2 in either the canine or human assays.

As mentioned above, COX-2 selectivity can be determined by ratio in terms of IC_{50} value of COX-1 inhibition to COX-2 inhibition. In general, it can be said that a compound showing a COX-1/COX-2 inhibition ratio of more than 5 has sufficient COX-2 selectivity.

The activity of an invention combination for treating cartilage damage and pain and/or inflammation may be determined by the procedures of Biological Methods 9 or 10 as described below.

BIOLOGICAL METHOD 9

Monosodium Iodoacetate-induced Osteoarthritis in Rat Model of Cartilage Damage ("MIA Rat"):

One end result of the induction of osteoarthritis in this model, as determined by histologic analysis, is the development of an osteoarthritic condition within the affected joint, as characterized by the loss of Toluidine blue staining and formation of osteophytes. Associated with the histologic changes is a concentration-dependent degradation of joint cartilage, as evidenced by affects on hind-paw weight distribution of the limb containing the affected joint, the presence of increased amounts of proteoglycan or hydroxyproline in the joint upon biochemical analysis, or histopathological analysis of the osteoarthritic lesions.

Generally, In the MIA Rat model on Day 0, the hind-paw weight differential between the right arthritic joint and the left healthy joint of male Wistar rats (150 g) are determined with an incapacitance tester, model 2KG (Linton Instrumentation, Norfolk, United Kingdom). The incapacitance tester has a chamber on top with an outwardly sloping front wall that supports a rat's front limbs, and two weight sensing pads, one for each hind paw, that facilitates this determination. Then the rats are anesthetized with isofluorine, and the right, hind leg knee joint is injected with 1.0 mg of mono-iodoacetate ("MIA") through the

infrapatellar ligament. Injection of MIA into the joint results in the inhibition of glycolysis and eventual death of surrounding chondrocytes. The rats are further administered either an invention combination such as a combination, comprising an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, or vehicle (in the instant case, water) daily for 14 days or 28 days. Both the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib are each independently, typically administered at a dose of 30 mg per kilogram of rat per day (30 mg/kg/day), but each component of the combination may independently be administered at other doses such as, for example, 10 mg/kg/day, 60 mg/kg/day, 90-mg/kg/day, or 100 mg/kg/day according to the requirements of the combination being studied. It is well within the level of ordinary skill in the pharmaceutical arts to determine a proper dosage of an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib in this model. Administration of the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, in this model is optionally by oral administration or intravenous administration via an osmotic pump. Further, administration of the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, may be simultaneous as a co-formulation of both drugs, simultaneous by way of independent formulations of each drug of the invention combination alone according to optimal drug delivery profiles, or non-simultaneous such as, sequential administration of an independent formulation of one drug followed by, after some pre-determined period of time, administration of an independent formulation of the other drug of the invention combination. After 7 and 14 days for a two-week study, or 7, 14, and 28 days for a four-week study, the hind-paw weight distribution is again determined. Typically, the animals administered

vehicle alone place greater weight on their unaffected left hind paw than on their right hind paw, while animals administered an invention combination show a more normal (i.e., more like a healthy animal) weight distribution between their hind paws. This change in weight distribution was proportional to the degree of joint cartilage damage. Percent inhibition of a change in hind paw joint function is calculated as the percent change in hind-paw weight distribution for treated animals versus control animals. For example, for a two week study,

Percent inhibition of a change in hind paw joint function

$$= \left[1 - \frac{(\Delta W_G)}{(\Delta W_C)}\right] X\ 100$$

wherein: ΔW_C is the hind-paw weight differential between the healthy left limb and the arthritic limb of the control animal administered vehicle alone, as measured on Day 14; and

ΔW_G is the hind-paw weight differential between the healthy left limb and the arthritic limb of the animal administered an invention combination, as measured on Day 14.

In order to measure biochemical or histopathological end points in the MIA Rat model, some of the animals in the above study may be sacrificed, and the amounts of free proteoglycan in both the osteoarthritic right knee joint and the contralateral left knee joint may be determined by biochemical analysis. The amount of free proteoglycan in the contralateral left knee joint provides a baseline value for the amount of free proteoglycan in a healthy joint. The amount of proteoglycan in the osteoarthritic right knee joint in animals administered an invention combination, and the amount of proteoglycan in the osteoarthritic right knee joint in animals administered vehicle alone, are independently compared to the amount of proteoglycan in the contralateral left knee joint. The amounts of proteoglycan lost in the osteoarthritic right knee joints are expressed as percent loss of proteoglycan compared to the contralateral left knee joint control. The percent inhibition of proteoglycan loss, may be calculated as {[(proteoglycan loss from joint (%) with vehicle) - (proteoglycan loss from joint with an invention combination)] ÷ (proteoglycan loss from joint (%) with vehicle)} × 100.

The MIA Rat data that are expected from the analysis of proteoglycan loss would establish that an invention combination is effective for inhibiting cartilage damage and inflammation and/or alleviating pain in mammalian patients, including human.

The results of these studies with oral dosing may be presented in tabular format in the columns labelled "IJFL (%+/- SEM)", wherein IJFL means Inhibition of Joint Function Limitation, "SDCES", wherein SDCES means Significant Decrease In Cartilage Erosion Severity, and "SIJWHLE", wherein SIJWHLE means Significant Increase in Joints Without Hind Limb Erosion.

The proportion of subjects without hind limb erosions may be analyzed via an *Exact Sequential Cochran-Armitage Trend* test (*SAS*® Institute, 1999). The Cochran-Armitage Trend test is employed when one wishes to determine whether the proportion of positive or "Yes" responders increases or decreases with increasing levels of treatment. For the particular study, it is expected that the number of animals without joint erosions increased with increasing dose.

The ridit analysis may be used to determine differences in overall erosion severity. This parameter takes into account both the erosion grade (0 = no erosion, I = erosion extending into the superficial or middle layers, or II = deep layer erosion), and area (small, medium and large, quantified by dividing the area of the largest erosion in each score into thirds) simultaneously. The analysis recognizes that each unit of severity is different, but does not assume a mathematical relationship between units.

Another animal model for measuring effects of an invention combination on cartilage damage and inflammation and/or pain is described below in Biological Method 10.

BIOLOGICAL METHOD 10

Induction of Experimental Osteoarthritis in Rabbit ("EOA in Rabbit"):

Normal rabbits are anaesthetized and anteromedial incisions of the right knees performed. The anterior cruciate ligaments are visualized and sectioned. The wounds are closed and the animals are housed in individual cages, exercised,

and fed ad libitum. Rabbits are given either vehicle (water) or an invention combination dosed three times per day with 30-mg/kg/dose or 10-mg/kg/dose. each independently determined for the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, but each drug of the combination may independently be administered at other doses such as, for example, 3 times 20 mg/kg/day or 3 times 60 mg/kg/day according to the requirements of the combination being studied. The rabbits are euthanized 8 weeks after surgery and the proximal end of the tibia and the distal end of the femur are removed from each animal.

Macroscopic Grading

The cartilage changes on the femoral condyles and tibial plateaus are graded separately under a dissecting microscope (Stereozoom, Bausch & Lomb, Rochester, NY). The depth of erosion is graded on a scale of 0 to 4 as follows: grade 0 = normal surface; Grade 1 = minimal fibrillation or a slight yellowish discoloration of the surface; Grade 2 = erosion extending into superficial or middle layers only; Grade 3 = erosion extending into deep layers; Grade 4 = erosion extending to subchondral bone. The surface area changes are measured and expressed in mm^2. Representative specimens may also be used for histologic grading (see below).

Histologic Grading

Histologic evaluation is performed on sagittal sections of cartilage from the lesional areas of the femoral condyle and tibial plateau. Serial sections (5 um) are prepared and stained with safranin-O. The severity of OA lesions is graded on a scale of 0 - 14 by two independent observers using the histologic-histochemical scale of Mankin *et al.* This scale evaluates the severity of OA lesions based on the loss of safranin-O staining (scale 0 - 4), cellular changes (scale 0 - 3), invasion of tidemark by blood vessels (scale 0 - 1) and structural changes (scale 0 - 6). On this latter scale, 0 indicates normal cartilage structure and 6 indicates erosion of the

cartilage down to the subchondral bone. The scoring system is based on the most severe histologic changes in the multiple sections.

Representative specimens of synovial membrane from the medial and lateral knee compartments are dissected from underlying tissues. The specimens are fixed, embedded, and sectioned (5 um) as above, and stained with hematoxylin-eosin. For each compartment, two synovial membrane specimens are examined for scoring purposes and the highest score from each compartment is retained. The average score is calculated and considered as a unit for the whole knee. The severity of synovitis is graded on a scale of 0 to 10 by two independent observers, adding the scores of 3 histologic criteria: synovial lining cell hyperplasia (scale 0 - 2); villous hyperplasia (scale 0 - 3); and degree of cellular infiltration by mononuclear and polymorphonuclear cells (scale 0 - 5): 0 indicates normal structure.

Statistical Analysis

Mean values and SEM is calculated and statistical analysis was done using the Mann-Whitney U-test.

The results of these studies would be expected to show that an invention combination would reduce the size of the lesion on the tibial plateaus, and perhaps the damage in the tibia or on the femoral condyles, as well as show pain alleviating effects if measured. In conclusion, these results would show that an invention combination would have significant inhibition effects on the damage to cartilage and pain.

The foregoing studies would establish that an invention combination is effective for the inhibition of cartilage damage and inflammation and/or alleviating pain, and thus useful for the treatment of osteoarthritis or rheumatoid arthritis in human, and other mammalian disorders. Such a treatment offers a distinct advantage over existing treatments that only modify pain or inflammation or and other secondary symptoms. The effectiveness of an invention combination in this model would indicate that the invention combination will have clinically useful effects in preventing and/or treating cartilage damage, pain and/or inflammation.

Administration according to the invention method of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, to a mammal to treat the diseases listed above is preferably, although not necessarily, accomplished by administering the compound, or a salt thereof, in a pharmaceutical dosage form.

A selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and the allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, can be prepared and administered according to the invention method in a wide variety of oral and parenteral pharmaceutical dosage forms. Thus, a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and the allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and the allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, can be administered by inhalation, for example, intranasally. Additionally, a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and the allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active components a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof. The active compounds generally are present in a concentration of about 5% to about 95% by weight of the formulation.

For preparing pharmaceutical compositions from a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and the allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, (i.e., the active components) pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations are

preferred. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. Powders suitable for intravenous administration or administration by injection may be lyophilized.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from about 5% to about 70%, total, of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing an appropriate quantity of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.01 to 1000 mg, preferably 1 to 500 mg according to the particular application and the potency of the active components. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents to treat the above-listed diseases, the allosteric inhibitors of MMP-13, or a pharmaceutically acceptable salt thereof, or a combination of the same with a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, are administered at a dose that is effective for treating at least one symptom of the disease or disorder being treated. The initial dosage of about 1 mg/kg to about 100 mg/kg daily of the active component will be effective. A daily dose range of about 25 mg/kg to about 75 mg/kg of the active component is preferred. The

dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the particular allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, being employed in the invention combination. Determination of the proper dosage for a particular situation is within the skill of the art as described above. Typical dosages will be from about 0.1 mg/kg to about 500 mg/kg, and ideally about 25 mg/kg to about 250 mg/kg, such that it will be an amount that is effective to treat the particular disease or disorder being treated.

A preferred composition for dogs comprises an ingestible liquid peroral dosage form selected from the group consisting of a solution, suspension, emulsion, inverse emulsion, elixir, extract, tincture and concentrate, optionally to be added to the drinking water of the dog being treated. Any of these liquid dosage forms, when formulated in accordance with methods well known in the art, can either be administered directly to the dog being treated, or may be added to the drinking water of the dog being treated. The concentrate liquid form, on the other hand, is formulated to be added first to a given amount of water, from which an aliquot amount may be withdrawn for administration directly to the dog or addition to the drinking water of the dog.

A preferred composition provides delayed-, sustained- and/or controlled-release of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, and the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof. Such preferred compositions include all such dosage forms which produce $\geq 40\%$ inhibition of cartilage degradation, and result in a plasma concentration of the active component of at least 3 fold the active component's ED_{40} for at least 2 hours; preferably for at least 4 hours; preferably for at least 8 hours; more preferably for at least 12 hours; more preferably still for at least 16 hours; even more preferably still for at least 20 hours; and most preferably for at least 24 hours. Preferably, there is included within the above-described dosage forms those which produce $\geq 40\%$ inhibition of cartilage degradation, and result in a plasma concentration of the active component of at least 5 fold the active component's ED_{40} for at least 2 hours,

preferably for at least 2 hours, preferably for at least 8 hours, more preferably for at least 12 hours, still more preferably for at least 20 hours and most preferably for at least 24 hours. More preferably, there is included the above-described dosage forms which produce ≥ 50% inhibition of cartilage degradation, and result in a plasma concentration of the active component of at least 5 fold the active component's ED_{40} for at least 2 hours, preferably for at least 4 hours, preferably for at least 8 hours, more preferably for at least 12 hours, still more preferably for at least 20 hours and most preferably for at least 24 hours.

The following Formulation Examples 1 to 8 illustrate the invention pharmaceutical compositions wherein the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, are formulated separately, each independently as described, When the formulations comprise the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient, they contain a cartilage damage treating effective amount or an anti-osteoarthritic effective amount of the allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof. When the formulations comprise a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, they contain a pain alleviating effective amount or an anti-inflammatory effective amount of the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof. The examples are representative only, and are not to be construed as limiting the invention in any respect.

FORMULATION EXAMPLE 1

Tablet Formulation:

Ingredient	Amount (mg)
An allosteric inhibitor of MMP-13, or a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

The allosteric inhibitor of MMP-13, or a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for inhibiting cartilage damage or treating osteoarthritis, or for alleviating pain or inhibiting inflammation.

FORMULATION EXAMPLE 2

Coated Tablets:

The tablets of Formulation Example 1 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

FORMULATION EXAMPLE 3

Injection vials:

The pH of a solution of 500 g of an allosteric inhibitor of MMP-13, or a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is

not celecoxib or valdecoxib, and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 25 mg of the allosteric inhibitor of MMP-13 or the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

FORMULATION EXAMPLE 4

Suppositories:

A mixture of 25 g of the allosteric inhibitor of MMP-13 or a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib that is not celecoxib or valdecoxib, 100 g of soya lecithin, and 1400 g of cocoa butter is fused, poured into molds, and allowed to cool. Each suppository contains 25 mg of the allosteric inhibitor of MMP-13 or the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

FORMULATION EXAMPLE 5

Solution:

A solution is prepared from 1 g of the allosteric inhibitor of MMP-13 or a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib 9.38 g of $NaH_2PO_4 \cdot 12H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$, and 0.1 g benzalkonium chloride in 940 mL of double-distilled water. The pH of the solution is adjusted to pH 6.8 using 2 M hydrochloric acid. The solution is diluted to 1.0 L with double-distilled water, and sterilized by irradiation. A 25 mL volume of the solution contains 25 mg of the allosteric inhibitor of MMP-13 or the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

FORMULATION EXAMPLE 6

Ointment:

500 mg of the allosteric inhibitor of MMP-13 or a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib is mixed with 99.5 g of petroleum jelly under aseptic conditions. A 5 g portion of the ointment contains 25 mg of the allosteric inhibitor of MMP-13 or the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

FORMULATION EXAMPLE 7

Capsules:

2 kg of the allosteric inhibitor of MMP-13 or a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the allosteric inhibitor of MMP-13 or the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib.

FORMULATION EXAMPLE 8

Ampoules:

A solution of 2.5 kg of the allosteric inhibitor of MMP-13 or a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof, that is not celecoxib or valdecoxib is dissolved in 60 L of double-distilled water. The solution is sterile filtered, and the filtrate is filled into ampoules. The ampoules are lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 25 mg of the allosteric inhibitor of MMP-13 or the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib.

The following Formulation Examples 9 to 16 illustrate the invention pharmaceutical compositions containing an invention combination in a single formulation with a pharmaceutically acceptable carrier, diluent, or excipient. The examples are representative only, and are not to be construed as limiting the invention in any respect.

FORMULATION EXAMPLE 9

Tablet Formulation:

Ingredient	Amount (mg)
An allosteric inhibitor of MMP-13	25
A selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib	20
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	120

The allosteric inhibitor of MMP-13, a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of one of the above-listed diseases.

FORMULATION EXAMPLE 10

Coated Tablets:

The tablets of Formulation Example 9 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

FORMULATION EXAMPLE 11

Injection vials:

The pH of a solution of 250 g of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib, 500 g

of an allosteric inhibitor of MMP-13, and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 12.5 mg of the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib, and 25 mg of the allosteric inhibitor of MMP-13.

FORMULATION EXAMPLE 12

Suppositories:

A mixture of 50 g of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib, 25 g of an allosteric inhibitor of MMP-13, 100 g of soya lecithin, and 1400 g of cocoa butter is fused, poured into molds, and allowed to cool. Each suppository contains 50 mg of the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and 25 mg of the allosteric inhibitor of MMP-13.

FORMULATION EXAMPLE 13

Solution:

A solution is prepared from 0.5 g of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib, 1 g of an allosteric inhibitor of MMP-13, 9.38 g of $NaH_2PO_4 \cdot 12H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$, and 0.1 g benzalkonium chloride in 940 mL of double-distilled water. The pH of the solution is adjusted to pH 6.8 using 2 M hydrochloric acid. The solution is diluted to 1.0 L with double-distilled water, and sterilized by irradiation. A 25 mL volume of the solution contains 12.5 mg of the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and 25 mg of the allosteric inhibitor of MMP-13.

FORMULATION EXAMPLE 14

Ointment:

100 mg of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib, 500 mg of an allosteric inhibitor of MMP-13, sodium salt, is mixed with 99.4 g of petroleum jelly under aseptic conditions. A 5 g portion of the ointment contains 5 mg of the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and 25 mg of the allosteric inhibitor of MMP-13 sodium salt.

FORMULATION EXAMPLE 15

Capsules:

2 kg of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and 20 kg of an allosteric inhibitor of MMP-13, hydrochloride salt, are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and 250 mg of the allosteric inhibitor of MMP-13 hydrochloride salt.

FORMULATION EXAMPLE 16

Ampoules:

A solution of 2.5 kg of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and 2.5 kg of an allosteric inhibitor of MMP-13 is dissolved in 60 L of double-distilled water. The solution is sterile filtered, and the filtrate is filled into ampoules. The ampoules are lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 25 mg each of the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and the allosteric inhibitor of MMP-13.

While it may be desirable to formulate a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof,

together in one capsule, tablet, ampoule, solution, and the like, for simultaneous administration, as discussed above, it is not necessary for the purposes of practicing the invention methods. A selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, of an invention combination alternatively can each be formulated independently in any form such as, those of any one Formulation Examples 1 to 16, and administered either simultaneously or at different times.

The following Formulation Examples 17 and 18 illustrate the invention pharmaceutical compositions containing discrete formulations of the active components of the invention combination and a pharmaceutically acceptable carrier, diluent, or excipient. The examples are representative only, and are not to be construed as limiting the invention in any respect.

FORMULATION EXAMPLE 17

Tablet Formulation of an allosteric inhibitor of MMP-13:

Ingredient	Amount (mg)
An allosteric inhibitor of MMP-13	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (paste)	10
Magnesium stearate (1%)	5
Total	100

An allosteric inhibitor of MMP-13, lactose, and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet.

Injection vial formulation of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib:

The pH of a solution of 500 g of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib and 5 g of disodium hydrogen phosphate is adjusted to pH 6.5 in 3 L of double-distilled water using 2 M hydrochloric acid. The solution is sterile filtered, and the filtrate is filled into injection vials, lyophilized under sterile conditions, and aseptically sealed. Each injection vial contains 25 mg of the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib.

Such tablets containing an allosteric inhibitor of MMP-13 can be administered to a human from one to four times a day for treatment of the above-listed diseases, and the injection solutions containing the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib can be administered to a human 1 or 2 times per day, wherein the administration by injection is optionally simultaneous with administration of the tablets or at different times, for the treatment of one of the above-listed diseases.

FORMULATION EXAMPLE 18

Coated Tablets containing an allosteric inhibitor of MMP-13:

The tablets of Formulation Example 17 are coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth, and colorant.

Capsules containing a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib:

2 kg of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib are filled into hard gelatin capsules in a customary manner such that each capsule contains 25 mg of the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib.

Such coated tablets containing an allosteric inhibitor of MMP-13 can be administered to a human from one to four times a day for treatment of the above-

listed diseases, and the capsules containing the selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib can be administered to a human 1 or 2 times per day, wherein the administration of the capsules is optionally simultaneous with administration of the tablets or at different times, for the treatment of one of the above-listed diseases.

Still further, it should be appreciated that the invention methods comprising administering an invention combination to a mammal to treat diseases or disorders listed above may be used to treat different diseases simultaneously. For example, administration of a selective inhibitor of COX-2, or a pharmaceutically acceptable salt thereof that is not celecoxib or valdecoxib in accordance with the invention combination may be carried out as described above to treat inflammation, arthritic pain, pain associated with menstrual cramping, and migraines, while an allosteric inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof, may be administered to treat OA or inhibit cartilage damage.

As shown above, the invention method offers a distinct advantage over existing treatments for diseases such as OA that comprise cartilage damage, wherein the existing treatments modify pain or secondary symptoms, but do not show a disease modifying effect.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

Having described the invention method, various embodiments of the invention are hereupon claimed.